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    16may02 14:54:16 User217743 Session D556.1
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   $0.00  Estimated cost FileHomeBase
   $0.00  Estimated cost this search
   $0.00  Estimated total session cost   0.164 DialUnits
File 410:Chronolog(R) 1981-2002/May
    (c) 2002 The Dialog Corporation

    Set  Items  Description
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HILIGHT set on as '%%%'%%%
%%%HILIGHT set on as '%%%'
? b 153
>>>       153 does not exist
>>>1 of the specified files is not available
>>>No valid files specified
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File 155:MEDLINE(R) 1966-2002/May W2
*File 155: This file has been reloaded. Accession numbers
have changed.
    Set  Items  Description
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? s gm()csf
       24495  GM
       41710  CSF
    S1   9321  GM()CSF
? s leukine
    S2     13  LEUKINE
? s sargramostim
    S3     71  SARGRAMOSTIM
? s s2 or s3
         13  S2
         71  S3
    S4     79  S2 OR S3
? s s4 and py>2001
         79  S4
     180293  PY>2001
    S5     10  S4 AND PY>2001
? s s5 not s4
         10  S5
         79  S4
    S6      0  S5 NOT S4
? s s4 not s5
         79  S4
         10  S5
    S7     69  S4 NOT S5
? t s7/3,ab/all

 7/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

12601059  21560200  PMID: 11704787
 Trafficking of CD34+ cells into the peripheral
circulation during collection of peripheral blood stem
cells by apheresis.
 Rowley S D; Yu J; Gooley T; Heimfeld S; Holmberg L;
Maloney D; Bensinger W I
 Clinical Research Division, Fred Hutchinson Cancer
Research Center, Seattle, WA, USA.
 Bone marrow transplantation (England) Oct 2001, 28
(7) p649-56, ISSN 0268-3369 Journal Code: 8702459
 Contract/Grant No.: CA15704; CA; NCI; CA18029; CA;
NCI
 Document type: Evaluation Studies; Journal Article
 Languages: ENGLISH
 Main Citation Owner: NLM
 Record type: Completed
 The number of CD34+ cells collected during apheresis
is related to the volume of blood processed. In
large-volume apheresis (LVL) procedure, more cells can be
collected than were originally present in the peripheral
blood at the start of the collection procedure. We
prospectively studied the levels of CD34+ cells in the
blood and apheresis product during LVL procedures for
21 patients with acute myelogenous leukemia or multiple
myeloma. These patients experienced a slow decline in
blood CD34+ cell concentrations during the apheresis
procedure. No patient demonstrated a sustained rise in
CD34+ cell counts as a result of the procedure. The
number of CD34+ cells collected exceeded the number
calculated to be in the peripheral blood at the start of
the procedure by an average of 3.0-fold. The efficiency
of collection for CD34+ cells averaged 92.6% and did not
vary with speed of blood processing, diagnosis, or
mobilization regimen. The calculated release of CD34+
cells from other reservoirs into the peripheral blood
averaged 3.71 x 10(6)/min (range, 0.36-13.7 x 10(6)/min),
and correlated (r = 0.82) with the concentration of
these cells in the peripheral blood at the start of the
procedure. These data show that the apheresis procedure
used in this study does not affect the release of CD34+
cells in a cytokine-treated patient. LVL will result in
collection of larger quantities of CD34+ cells than
procedures involving processing of smaller volumes of
blood, but the number of cells collected is limited by the
rate of release of these cells into the peripheral
circulation where they are accessible for collection.


 7/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

12588560  21474076  PMID: 11590502
   Use of %%%sargramostim%%% (rh-GM-CSF) as
adjunctive treatment of fluconazole-refractory
oropharyngeal candidiasis in patients with AIDS: a pilot
study.
 Vazquez J A; Hidalgo J A; De Bono S
 Department of Medicine, Division of Infectious
```

Diseases, Wayne State University School of Medicine, Detroit, Michigan, USA.
HIV clinical trials (United States) Nov-Dec 2000, 1 (3) p23-9, ISSN 1528-4336 Journal Code: 100936377
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Fluconazole-refractory mucosal candidiasis is a significant problem in patients with advanced HIV disease. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is postulated to activate neutrophils, enhance phagocytosis, and increase intracellular killing of Candida species. The aim of this study was to evaluate the use of %%%sargramostim%%% (rh-GM-CSF) in combination with fluconazole for refractory mucosal candidiasis in patients with AIDS. METHOD: Patients with mycologically confirmed fluconazole-refractory oropharyngeal candidiasis who failed fluconazole 400 mg/day for a minimum of 7 days were enrolled, continued on fluconazole (400 mg/day), and received %%%sargramostim%%% 2.5 microg/kg/day for a minimum of 2 weeks. Patients were evaluated for clinical signs and symptoms of oropharyngeal candidiasis, and quantitative fungal cultures were taken at baseline and the end of weeks 1 and 2 of therapy. RESULTS: Eleven patients were entered, 3 out of 11 patients were cured, 6 were unchanged, and 2 were worse at the 2-week evaluation. Mycological response was seen in 7 out of 11 patients. CONCLUSION: In this small pilot study, %%%sargramostim%%% appears to exert a beneficial effect on the mucosal mycoflora and may be a possible alternative as adjunctive therapy in the management of fluconazole-refractory mucosal candidiasis in advanced HIV-positive patients.

7/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

11283018 21328734 PMID: 11436117
Mobilization of peripheral blood stem cells following myelosuppressive chemotherapy: a randomized comparison of filgrastim, %%%sargramostim%%%, or sequential %%%sargramostim%%% and filgrastim.
Weaver C H; Schulman K A; Buckner C D
CancerConsultants.com Inc., Ketchum, ID, USA.
Bone marrow transplantation (England) May 2001, 27 Suppl 2 pS23-9, ISSN 0268-3369 Journal Code: 8702459
Document type: Clinical Trial; Clinical Trial, Phase III; Journal Article ; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Myelosuppressive chemotherapy is frequently used for mobilization of autologous CD34(+) progenitor cells into the peripheral blood for subsequent collection and support of high-dose chemotherapy. The administration of myelosuppressive chemotherapy is typically followed by a myeloid growth factor and is associated with variable CD34 cell yields and morbidity. The two most commonly used myeloid growth factors for facilitation of CD34 cell harvests are granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). We performed a randomized phase III clinical trial comparing G-CSF, GM-CSF, and sequential administration of GM-CSF and G-CSF following administration of myelosuppressive chemotherapy. We evaluated CD34 yields, morbidity, and cost-effectiveness of the three cytokine schedules. One hundred and fifty-six patients with multiple myeloma, breast cancer, or lymphoma received cyclophosphamide with either paclitaxel or etoposide and were randomized to receive G-CSF 6 microg/kg/day s.c., GM-CSF 250 microg/m(2)/day s.c., or GM-CSF for 6 days followed by G-CSF until completion of the stem cell harvest. Compared with patients who received GM-CSF, patients who received G-CSF had faster recovery of absolute neutrophil count to 0.5 x 10(9) per liter (median of 11 vs14 days, P = 0.0001) with fewer patients requiring red blood cell transfusions (P= 0.008); fewer patients with fever (18% vs 52%, P = 0.001); fewer hospital admissions (20% vs 42%, P = 0.13); and less intravenous antibiotic therapy (24% vs 59%, P = 0.001). Patients who received G-CSF also yielded more CD34 cells (median 7.1 vs 2.0 x 10(6) kg per apheresis, P = 0.0001) and a higher percentage achieved 2.5 x 10(6) CD34 cells per kilogram (94% vs 78%, P = 0.21) and 5 x 10(6) CD34 cells per kilogram (88% vs 53%, P = 0.01) or more CD34 cells per kilogram with fewer aphereses (median 2 vs 3, P = 0.002) and fewer days of growth factor treatment (median 12 vs 14, P = 0.0001). There were no significant differences in outcomes between groups receiving G-CSF alone and the sequential regimen. After high-dose chemotherapy, patients who had peripheral blood stem cells mobilized with G-CSF or the sequential regimen received higher numbers of CD34 cells and had faster platelet recovery with fewer patients requiring platelet transfusions than patients receiving peripheral blood stem cells mobilized by GM-CSF. In summary, G-CSF alone is superior to GM-CSF alone for the mobilization of CD34(+) cells and reduction of toxicities following myelosuppressive chemotherapy. An economic analysis evaluating the cost-effectiveness of these three effective schedules is ongoing at the time of this writing.

7/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

11250614 21319780 PMID: 11426487
Phase II study of combination human recombinant GM-CSF with intermediate-dose cytarabine and mitoxantrone chemotherapy in patients with high-risk

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ERROR: syntaxerror
OFFENDING COMMAND:           ,$$      1       -         /   *

STACK:

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   $0.00  Estimated cost this search
   $0.00  Estimated total session cost   0.164 DialUnits
File 410:Chronolog(R) 1981-2002/May
    (c) 2002 The Dialog Corporation

    Set  Items  Description
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HILIGHT set on as '*'*
*HILIGHT set on as '*'
? b 153
>>>       153 does not exist
>>>1 of the specified files is not available
>>>No valid files specified
? b 155
    16may02 14:54:52 User217743 Session D556.2
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   $0.12  TELNET
   $0.12  Estimated cost this search
   $0.12  Estimated total session cost   0.304 DialUnits
File 155:MEDLINE(R) 1966-2002/May W2
*File 155: This file has been reloaded. Accession numbers
have changed.
    Set  Items  Description
    ---  -----  -----------
? s gm()csf
       24495  GM
       41710  CSF
    S1   9321  GM()CSF
? s leukine
    S2     13  LEUKINE
? s sargramostim
    S3     71  SARGRAMOSTIM
? s s2 or s3
         13  S2
         71  S3
    S4     79  S2 OR S3
? s s4 and py>2001
         79  S4
     180293  PY>2001
    S5     10  S4 AND PY>2001
? s s5 not s4
         10  S5
         79  S4
    S6      0  S5 NOT S4
? s s4 not s5
         79  S4
         10  S5
    S7     69  S4 NOT S5
? t s7/3,ab/all

 7/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

12601059  21560200  PMID: 11704787
 Trafficking of CD34+ cells into the peripheral
circulation during collection of peripheral blood stem
cells by apheresis.
 Rowley S D; Yu J; Gooley T; Heimfeld S; Holmberg L;
Maloney D; Bensinger W I
 Clinical Research Division, Fred Hutchinson Cancer
Research Center, Seattle, WA, USA.
 Bone marrow transplantation (England) Oct 2001, 28
(7) p649-56, ISSN 0268-3369 Journal Code: 8702459
 Contract/Grant No.: CA15704; CA; NCI; CA18029; CA;
NCI
 Document type: Evaluation Studies; Journal Article
 Languages: ENGLISH
 Main Citation Owner: NLM
 Record type: Completed
 The number of CD34+ cells collected during apheresis
is related to the volume of blood processed. In
large-volume apheresis (LVL) procedure, more cells can be
collected than were originally present in the peripheral
blood at the start of the collection procedure. We
prospectively studied the levels of CD34+ cells in the
blood and apheresis product during LVL procedures for
21 patients with acute myelogenous leukemia or multiple
myeloma. These patients experienced a slow decline in
blood CD34+ cell concentrations during the apheresis
procedure. No patient demonstrated a sustained rise in
CD34+ cell counts as a result of the procedure. The
number of CD34+ cells collected exceeded the number
calculated to be in the peripheral blood at the start of
the procedure by an average of 3.0-fold. The efficiency
of collection for CD34+ cells averaged 92.6% and did not
vary with speed of blood processing, diagnosis, or
mobilization regimen. The calculated release of CD34+
cells from other reservoirs into the peripheral blood
averaged 3.71 x 10(6)/min (range, 0.36-13.7 x 10(6)/min),
and correlated (r = 0.82) with the concentration of
these cells in the peripheral blood at the start of the
procedure. These data show that the apheresis procedure
used in this study does not affect the release of CD34+
cells in a cytokine-treated patient. LVL will result in
collection of larger quantities of CD34+ cells than
procedures involving processing of smaller volumes of
blood, but the number of cells collected is limited by the
rate of release of these cells into the peripheral
circulation where they are accessible for collection.


 7/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

12588560  21474076  PMID: 11590502
  Use of *sargramostim* (rh-GM-CSF) as adjunctive
treatment of fluconazole-refractory oropharyngeal
candidiasis in patients with AIDS: a pilot study.
 Vazquez J A; Hidalgo J A; De Bono S
 Department of Medicine, Division of Infectious
Diseases, Wayne State University School of Medicine,
```

Detroit, Michigan, USA.
HIV clinical trials (United States) Nov-Dec 2000, 1 (3) p23-9, ISSN 1528-4336 Journal Code: 100936377
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Fluconazole-refractory mucosal candidiasis is a significant problem in patients with advanced HIV disease. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is postulated to activate neutrophils, enhance phagocytosis, and increase intracellular killing of Candida species. The aim of this study was to evaluate the use of *sargramostim* (rh-GM-CSF) in combination with fluconazole for refractory mucosal candidiasis in patients with AIDS. METHOD: Patients with mycologically confirmed fluconazole-refractory oropharyngeal candidiasis who failed fluconazole 400 mg/day for a minimum of 7 days were enrolled, continued on fluconazole (400 mg/day), and received *sargramostim* 2.5 microg/kg/day for a minimum of 2 weeks. Patients were evaluated for clinical signs and symptoms of oropharyngeal candidiasis, and quantitative fungal cultures were taken at baseline and the end of weeks 1 and 2 of therapy. RESULTS: Eleven patients were entered, 3 out of 11 patients were cured, 6 were unchanged, and 2 were worse at the 2-week evaluation. Mycological response was seen in 7 out of 11 patients. CONCLUSION: In this small pilot study, *sargramostim* appears to exert a beneficial effect on the mucosal mycoflora and may be a possible alternative as adjunctive therapy in the management of fluconazole-refractory mucosal candidiasis in advanced HIV-positive patients.

7/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

11283018 21328734 PMID: 11436117
Mobilization of peripheral blood stem cells following myelosuppressive chemotherapy: a randomized comparison of filgrastim, *sargramostim*, or sequential *sargramostim* and filgrastim.
Weaver C H; Schulman K A; Buckner C D
CancerConsultants.com Inc., Ketchum, ID, USA.
Bone marrow transplantation (England) May 2001, 27 Suppl 2 pS23-9, ISSN 0268-3369 Journal Code: 8702459
Document type: Clinical Trial; Clinical Trial, Phase III; Journal Article ; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Myelosuppressive chemotherapy is frequently used for mobilization of autologous CD34(+) progenitor cells into the peripheral blood for subsequent collection and support of high-dose chemotherapy. The administration of myelosuppressive chemotherapy is typically followed by a myeloid growth factor and is associated with variable CD34 cell yields and morbidity. The two most commonly used myeloid growth factors for facilitation of CD34 cell harvests are granulocyte colony-stimulating factor (G-CSF) and granulocyte-macrophage colony-stimulating factor (GM-CSF). We performed a randomized phase III clinical trial comparing G-CSF, GM-CSF, and sequential administration of GM-CSF and G-CSF following administration of myelosuppressive chemotherapy. We evaluated CD34 yields, morbidity, and cost-effectiveness of the three cytokine schedules. One hundred and fifty-six patients with multiple myeloma, breast cancer, or lymphoma received cyclophosphamide with either paclitaxel or etoposide and were randomized to receive G-CSF 6 microg/kg/day s.c., GM-CSF 250 microg/m(2)/day s.c., or GM-CSF for 6 days followed by G-CSF until completion of the stem cell harvest. Compared with patients who received GM-CSF, patients who received G-CSF had faster recovery of absolute neutrophil count to 0.5 x 10(9) per liter (median of 11 vs14 days, P = 0.0001) with fewer patients requiring red blood cell transfusions (P= 0.008); fewer patients with fever (18% vs 52%, P = 0.001); fewer hospital admissions (20% vs 42%, P = 0.13); and less intravenous antibiotic therapy (24% vs 59%, P = 0.001). Patients who received G-CSF also yielded more CD34 cells (median 7.1 vs 2.0 x 10(6) kg per apheresis, P = 0.0001) and a higher percentage achieved 2.5 x 10(6) CD34 cells per kilogram (94% vs 78%, P = 0.21) and 5 x 10(6) CD34 cells per kilogram (88% vs 53%, P = 0.01) or more CD34 cells per kilogram with fewer aphereses (median 2 vs 3, P = 0.002) and fewer days of growth factor treatment (median 12 vs 14, P = 0.0001). There were no significant differences in outcomes between groups receiving G-CSF alone and the sequential regimen. After high-dose chemotherapy, patients who had peripheral blood stem cells mobilized with G-CSF or the sequential regimen received higher numbers of CD34 cells and had faster platelet recovery with fewer patients requiring platelet transfusions than patients receiving peripheral blood stem cells mobilized by GM-CSF. In summary, G-CSF alone is superior to GM-CSF alone for the mobilization of CD34(+) cells and reduction of toxicities following myelosuppressive chemotherapy. An economic analysis evaluating the cost-effectiveness of these three effective schedules is ongoing at the time of this writing.

7/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

11250614 21319780 PMID: 11426487
Phase II study of combination human recombinant GM-CSF with intermediate-dose cytarabine and mitoxantrone chemotherapy in patients with high-risk myelodysplastic syndromes (RAEB, RAEBT, and CMML): an Eastern Cooperative Oncology Group Study.

Bennett J M; Young M S; Liesveld J L; Paietta E; Miller K B; Lazarus H M; Marsh R D; Friedenberg W R; Saba H T; Hayes F A; Dewald G W; Hiddemann W; Rowe J M

University of Rochester Cancer Center, New York 14642, USA. john bennett@urmc.rochester.edu

American journal of hematology (United States) Jan 2001, 66 (1) p23-7, ISSN 0361-8609 Journal Code: 7610369

Contract/Grant No.: CA07190; CA; NCI; CA11083; CA; NCI; CA23318; CA; NCI; +

Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article; Multicenter Study

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

A Phase II study of GM-CSF with intermediate-dose cytarabine and mitoxantrone was conducted in patients with high-risk myelodysplastic syndrome. It was designed to evaluate if priming with growth factor could increase the efficiency of chemotherapy. In this older population only two of 10 patients achieved a bone marrow CR, including one patient whose leukemic blasts had an "S" phase increase of 2.55x at 48 hr. Unexpected hepatotoxicity was noted. This regimen cannot be recommended for this elderly population of patients.

7/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

11227562 21259855 PMID: 11359669

Colony-stimulating factors in stem cell transplantation: effect on quality of life.

Godder K T; Henslee-Downey P J

Division of Transplantation Medicine, Palmetto Richland Memorial Hospital and University of South Carolina, Columbia, SC 29203, USA. kgodder@earthlink.net

Journal of hematotherapy & stem cell research (United States) Apr 2001, 10 (2) p215-28, ISSN 1525-8165 Journal Code: 100892915 Document type: Journal Article; Review; Review, Academic Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Health-related quality of life (QOL) is poorest during the immediate post-transplantation period, but the impact of medical interventions during this period has not been studied. Colony-stimulating factors (CSFs), which are used to minimize short-term negative outcomes, might be expected to improve QOL; however, little is published about their impact on QOL during this period. We conducted a MEDLINE search to identify studies reporting on outcomes of stem cell transplantation (SCT) affected by the CSFs, mainly *sargramostim* and filgrastim. End points studied were: mucositis, incidence and type of infection, duration of hospitalization, time to myeloid engraftment, and quantity and quality of harvested cells. To impute the impact of CSFs on QOL post-SCT, we also reviewed the association between QOL and CSF outcomes in other circumstances. Data suggest that both CSFs improve QOL in the early autologous or allogeneic post-bone marrow transplantation period. Poor QOL caused by infection and increased length of hospital stay is expected to be improved by *sargramostim*. Time to myeloid engraftment, when negatively affecting QOL, is expected to be improved with both CSFs; however, the time to myeloid engraftment is consistently shorter with filgrastim. Current prospective trials designed to study the effects of CSFs in the immediate post-SCT period should collect QOL data.

7/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

11150669 21175027 PMID: 11279797

Treatment of kidney cancer with autologous tumor cell vaccines of short-term cell lines derived from renal cell carcinoma.

Dillman R O; Barth N M; VanderMolen L A; Garfield D H; De Leon C; O'Connor A A; Mahdavi K; Nayak S K

Hoag Cancer Center, One Hoag Drive, Building 41, Newport Beach, California 92658, USA. rdillman@hoaghospital.org

Cancer biotherapy & radiopharmaceuticals (United States) Feb 2001, 16 (1) p47-54, ISSN 1084-9785 Journal Code: 9605408

Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article; Randomized Controlled Trial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

BACKGROUND: We established short-term cultures of autologous tumors from patients with renal carcinoma for use as active specific immunotherapy (i.e., autologous vaccine). METHODS: Between 9/91 and 9/99 the cell biology laboratory of the Hoag Cancer Center received 69 kidney tumor samples that had been surgically excised, including 43 primary tumors and 26 metastatic lesions. Efforts were made to establish short-term tumor cell cultures to use as autologous tumor cell vaccines. Prior to treatment, patients underwent a baseline skin test for delayed tumor hypersensitivity (DTH) and then received s.c. injections of 10 million irradiated tumor cells that were given with various adjuvants weekly x3 and then monthly x5. RESULTS: Cell lines were established for 55/69 patients (80%) including 36/43 (84%) from primary tumors and 19/26 (73%) from distant metastases. Vaccines were prepared for 41 patients; 27 were treated. At the time of this analysis, follow up data was available for 26 patients with a median follow up > 5 years. Treatment was well-tolerated. Of 10 patients who had no evident disease at the time of treatment, nine were alive 1-8 years later; 5/8 had conversion of their DTH test from negative to positive. For 16 patients with measurable

metastatic disease at the time of treatment, there were no objective tumor responses; their median survival was 5.0 months. Among these 16 patients, only 1/8 DTH tests converted, but three had a positive baseline DTH test; one was previously treated with interleukin-2 and tumor infiltrating lymphocytes and two others were previously treated with autolymphocyte therapy. CONCLUSIONS: Vaccine therapy with short-term cultures of autologous tumor cells is feasible, well-tolerated and associated with conversion of DTH and long-term survival in patients who are free of disease at the time treatment is initiated. However, significant anti-tumor responses were not seen in patients with measurable disease at the time vaccine treatment was initiated.

7/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

11052250 21041407 PMID: 11197591
Efficacy of colony-stimulating factors in acute leukemia.
Holdsworth M T; Mathew P
College of Pharmacy and Department of Pediatrics, University of New Mexico, Albuquerque, NM 87131-5691, USA. markt@unm.edu
Annals of pharmacotherapy (United States) Jan 2001, 35 (1) p92-108, ISSN 1060-0280 Journal Code: 9203131
Comment in Ann Pharmacother. 2001 Jan;35(1) 120-2; Comment in PMID 11197572
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To evaluate the literature describing the safety and efficacy of the hematopoietic colony-stimulating factors (CSFs) for the management of treatment-related adverse effects in patients with acute leukemia. DATA SOURCES: A systematic MEDLINE search of the English-language literature (1995-April 2000) was performed to identify all randomized trials evaluating CSF use in acute leukemia. The following search terms were used: granulocyte colony-stimulating factor, filgrastim, granulocyte-macrophage colony-stimulating factor, *sargramostim*, acute lymphoblastic leukemia (ALL), acute myelogenous leukemia (AML), acute nonlymphocytic leukemia, and acute myeloid leukemia. The references from relevant literature were also examined in order to identify reports not discovered in the MEDLINE search. DATA SYNTHESIS: Six randomized trials in pediatric ALL, nine in adult AML, and four in adult ALL have examined the safety and efficacy of the CSFs. Two of the pediatric trials supported a reduction in either the duration of hospitalization or in the incidence of febrile neutropenia when a CSF was employed during the consolidation or intensification phase of chemotherapy. The remaining pediatric trials failed to demonstrate a clinical benefit. In adult AML, eight of the nine trials showed a significant decrease in the time to neutrophil recovery when a CSF was used. Only one of these trials demonstrated a decrease in hospital stay and none showed a decreased incidence of infection for patients who received a CSF. Three of the four trials in adult ALL demonstrated the efficacy of a CSF in decreasing the number of days to neutrophil recovery. Only one trial demonstrated that a CSF led to a reduction in the number of hospital days. Trials in children or adults have not demonstrated that the CSFs influence the long-term outcome of patients with acute leukemia. CONCLUSIONS: The published studies document a decrease in the time to recovery from neutropenia when patients with acute leukemia are treated with a CSF. However, a consistent reduction in infectious complications or in the duration of hospitalization has not been demonstrated when a CSF is used for either pediatric or adult patients. Very limited data exist to support the premise that CSFs meet the criteria established by the American Society of Clinical Oncology for demonstrating the value of these agents. Further careful study focused on resource utilization and pharmacoeconomics may help to elucidate how healthcare institutions may most effectively employ CSFs to treat patients with acute leukemia.

7/3,AB/8
DIALOG(R)File 155:MEDLINE(R)

11037991 20701230 PMID: 11367364
In brief: immune based therapies.
PI perspective (UNITED STATES) Sep 1999, (No 28) p24, ISSN 1058-7454 Journal Code: 9102818
Document type: Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed
A study of HIV-1 Immunogen (Remune) has been recommended for closure by the Data Safety and Monitoring Board (DSMB), which monitors the safety of a study. A review of data by the DSMB determined that there was no difference in the rates of opportunistic infections and deaths between volunteers receiving Remune and those receiving a placebo. A new study has begun to see if Remune affects viral load or durability of HAART. Also discussed is a study of GM-CSF (*Leukine*), which ended with inconclusive findings. There was no difference in the development of opportunistic infections in volunteers receiving GM-CSF compared to volunteers receiving a placebo. However, those who received GM-CSF were more likely to have greater viral suppression than those receiving the placebo. The significance of this finding is unclear.

7/3,AB/9
DIALOG(R)File 155:MEDLINE(R)

11037430 20700665 PMID: 11366803
Leukine studies move forward.
Vazquez E
Positively aware : the monthly journal of the Test Positive Aware Network (UNITED STATES) Jul-Aug 1999, 10 (4) p29, ISSN 1523-2883 Journal Code: 9413754
Document type: Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed
A Phase III *Leukine* (sargramostium, GM-CSF) trial was completed. People who took the drug, while not having fewer AIDS-defining events, did have fewer infections and deaths. Some participants also experienced longer viral suppression, and almost all doubled their T-cells. *Leukine* injections were given three times weekly for 6 months. Side effects include injection site reactions and weight loss.

7/3,AB/10
DIALOG(R)File 155:MEDLINE(R)

11037346 20700582 PMID: 11366719
Summaries from the Eleventh Annual Houston Conference on AIDS in America. Research initiative, treatment action : RITA (UNITED STATES) Jul 1 1999, 5 (3) p13-25, ISSN 1520-8745 Journal Code: 100891089 Document type: Directory; Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed
A number of significant papers from the Eleventh Annual Houston Conference on AIDS in America are summarized. Topics include the current concepts in pathogenesis of HIV infection, the use of anti-HIV therapies, and drug interactions in HIV treatment. A session on HIV disease in children focused on the epidemiology and prevention of vertical transmission with Zidovudine, when to initiate therapy, and options for children who have failed current therapies. Studies using immune-based therapy have shown promise in treating HIV disease. New data from a study with *sargramostim*, an investigational agent for opportunistic infection prophylaxis, shows that the drug reduces viral loads and delays time to treatment failure. Pentafuside (T-20), the first of a new class of HIV drugs, fusion inhibitors, has been found to be safe and effective against HIV, although drug resistance may be associated with its use. Other sessions summarized progress in clearing HIV from viral reservoirs, the ethics of HIV research support from the drug industry and drug marketing, and a review of immune reconstitution studies among people on antiretroviral therapy. Sam Avrett of the AIDS Vaccine Advocacy Coalition (AVAC) summarized in his session the characteristics of a successful HIV vaccine and the need to have more people involved in vaccine advocacy as a means to ending the epidemic. Contact information is provided.

7/3,AB/11
DIALOG(R)File 155:MEDLINE(R)

11020333 21012399 PMID: 11130215
Comparative safety of filgrastim versus *sargramostim* in patients receiving myelosuppressive chemotherapy.
Milkovich G; Moleski R J; Reitan J F; Dunning D M; Gibson G A; Paivanas T A; Wyant S; Jacobs R J
School of Pharmacy, Medical College of Virginia, Richmond, USA. Pharmacotherapy (United States) Dec 2000, 20 (12) p1432-40, ISSN 0277-0008 Journal Code: 8111305
Document type: Journal Article; Multicenter Study
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
STUDY OBJECTIVE: To compare rates of adverse events with filgrastim versus *sargramostim* when given prophylactically to patients receiving myelosuppressive chemotherapy. DESIGN: Retrospective review with center crossover. SETTING: Ten United States outpatient chemotherapy centers. PATIENTS: Four hundred ninety patients treated for lung, breast, lymphatic system, or ovarian tumors. INTERVENTION: Prophylactic use of filgrastim or *sargramostim*, with dosages at investigator discretion. MEASUREMENTS AND MAIN RESULTS: The frequency and severity of adverse events and the frequency of switching to the alternative CSF were assessed. There was no difference in infectious fever. Fever unexplained by infection was more common with *sargramostim* (7% vs 1%, $p<0.001$), as were fatigue, diarrhea, injection site reactions, other dermatologic disorders, and edema (all $p<0.05$). Skeletal pain was more frequent with filgrastim ($p=0.06$). Patients treated with *sargramostim* switched to the alternative agent more often ($p<0.001$). CONCLUSION: Adverse events were less frequent with filgrastim than with *sargramostim*, suggesting that quality of life and treatment costs also may differ.

7/3,AB/12
DIALOG(R)File 155:MEDLINE(R)

10943420 20478007 PMID: 11023477
A randomized, placebo-controlled trial of granulocyte-macrophage colony-stimulating factor and

nucleoside analogue therapy in AIDS. Brites C; Gilbert M J; Pedral-Sampaio D; Bahia F; Pedroso C; Alcantara A P; Sasaki M D; Matos J; Renjifo B; Essex M; Whitmore J B; Agosti J M; Badaro R

Universidade Federal da Bahia and 2Hospital Sao Rafael, Salvador, Bahia, Brazil.

Journal of infectious diseases (UNITED STATES) Nov 2000, 182 (5) p1531-5, ISSN 0022-1899 Journal Code: 0413675

Document type: Clinical Trial; Journal Article; Randomized Controlled Trial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Preliminary preclinical and clinical data suggest that granulocyte-macrophage colony-stimulating factor (GM-CSF) may decrease viral replication. Therefore, 105 individuals with AIDS who were receiving nucleoside analogue therapy were enrolled in a placebo-controlled, double-blind study and were randomized to receive either 125 microgram/m(2) of yeast-derived, GM-CSF (*sargramostim*) or placebo subcutaneously twice weekly for 6 months. Subjects were evaluated for toxicity and disease progression. A significant decrease in mean virus load (VL) was observed for the GM-CSF treatment group at 6 months (-0.07 log(10) vs. -0.60 log(10); P=.02). More subjects achieved human immunodeficiency virus (HIV)-RNA levels <500 copies/mL at >/=2 evaluations (2% on placebo vs. 11% on GM-CSF; P=.04). Genotypic analysis of 46 subjects demonstrated a lower frequency of zidovudine-resistant mutations among those receiving GM-CSF (80% vs. 50%; P=.04). No difference was observed in the incidence of opportunistic infections (OIs) through 6 months or survival, despite a higher risk for OI among GM-CSF recipients. GM-CSF reduced VL and limited the evolution of zidovudine-resistant genotypes, potentially providing adjunctive therapy in HIV disease.

7/3,AB/13
DIALOG(R)File 155:MEDLINE(R)

10823611 20350866 PMID: 10894368

Evaluation of pre-radiotherapy cyclophosphamide in patients with newly diagnosed glioblastoma multiforme. Writing Committee for The Brain Tumor Center at Duke.

Bottom K S; Ashley D M; Friedman H S; Longee D C

The Department of Pediatrics, Duke University Medical Center, Durham, NC 27710, USA.

Journal of neuro-oncology (NETHERLANDS) 2000, 46 (2) p151-6, ISSN 0167-594X Journal Code: 8309335

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Cyclophosphamide is an alkylating agent that has shown activity in the treatment of pediatric brain tumors, including high-grade gliomas. This study was designed to evaluate the response of patients with newly diagnosed glioblastoma multiforme to pre-radiotherapy cyclophosphamide. Fourteen patients with glioblastoma multiforme were treated with high-dose cyclophosphamide (2 g/m2/day for 2 doses every 28 days) followed by either *sargramostim* or filgrastin. *Sargramostim* was given 250 microg/m2 subcutaneously twice a day continuing through the leukocyte nadir until the absolute neutrophil count was more than 1000 cells/microl for 2 consecutive days. The filgrastin dose was 10 microg/kg given subcutaneously once daily until the post nadir absolute neutrophil count was > or = 10,000 cells/microl. A total of 46 courses was given. Four patients received a total of 3 courses, 7 patients completed 4 courses and 3 patients received 2 courses. Three patients demonstrated complete response; 3 stable disease; and 8 progressive disease. The most common toxicity was hematologic, requiring platelet and packed red blood cell transfusions, with 13 admissions for neutropenia with fever. There were no deaths related to infection or bleeding. These results suggest that high-dose cyclophosphamide has modest activity with acceptable toxicity against newly diagnosed glioblastoma multiforme.

7/3,AB/14
DIALOG(R)File 155:MEDLINE(R)

10804043 20355113 PMID: 10894866

Randomized phase III study comparing conventional-dose doxorubicin plus ifosfamide versus high-dose doxorubicin plus ifosfamide plus recombinant human granulocyte-macrophage colony-stimulating factor in advanced soft tissue sarcomas: A trial of the European Organization for Research and Treatment of Cancer/Soft Tissue and Bone Sarcoma Group.

Le Cesne A; Judson I; Crowther D; Rodenhuis S; Keizer H J; Van Hoesel Q; Blay J Y; Frisch J; Van Glabbeke M; Hermans C; Van Oosterom A; Tursz T; Verweij J

Institut Gustave Roussy, Villejuif, London, United Kingdom. lecesne@igr.fr

Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Jul 2000, 18 (14) p2676-84, ISSN 0732-183X Journal Code: 8309333

Document type: Clinical Trial; Clinical Trial, Phase III; Journal Article ; Multicenter Study; Randomized Controlled Trial

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

PURPOSE: This randomized multicenter study was designed to compare the activity of a high-dose doxorubicin-containing chemotherapy regimen with a conventional standard-dose regimen in adult patients

with advanced soft tissue sarcomas (ASTS). PATIENTS AND METHODS: Between 1992 and 1995, 314 patients were randomized to receive a standard-dose regimen (arm A), containing doxorubicin (50 mg/m(2) on day 1) and ifosfamide (5 g/m(2) on day 1), or an intensified regimen (arm B), combining doxorubicin (75 mg/m(2) on day 1), the same ifosfamide dose, and recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF; *sargramostim* **, 250 microgram/m(2) on days 3 to 16); all courses were repeated every 3 weeks. RESULTS: The median age of the 294 eligible patients was 50 years. They received a median of five chemotherapy cycles. The median dose and relative doxorubicin dose-intensity achieved were 245 mg and 97% in arm A and 360 mg and 99% in arm B, respectively. Thirty-eight percent and 23% of patients presented with leiomyosarcomas and liver metastases, respectively. Objective responses were observed in 31 (21%) of 147 assessable patients in arm A and in 31 (23.3%) of 133 in arm B (P =.65). No change was observed in 41.6% and 46.2% of patients in arm A and B, respectively. Progression-free survival (PFS) was significantly longer in the intensive arm (P =.03). The median duration of the time to progression was 19 weeks in the conventional arm and 29 weeks in the intensified arm. There was no difference in overall survival (P =.98) between the two therapeutic arms. Toxicities were manageable in both arms. A grade 3/4 neutropenia and infection occurred in 92% and 4.6% of patients in arm A, respectively, and in 90% and 16.6% in arm B, respectively. Grade 3/4 thrombocytopenia was more frequent in arm B. CONCLUSION: The use of rhGM-CSF allowed safe escalation of chemotherapy doses. Despite a 50% increase of the doxorubicin dose-intensity, the high-dose regimen failed to demonstrate any impact on survival in patients with ASTS. The low complete response rate, the high incidence of leiomyosarcomas, and liver metastases may in part explain these results. However, the lengthening of the PFS in the intensive arm, because of the quality of stable disease and inappropriate tumor evaluation policies that potentially lead to an underestimation of antitumor activity, does not definitively refute the use of a high-dose chemotherapy regimen in selected patients with ASTS.

7/3,AB/15
DIALOG(R)File 155:MEDLINE(R)

10723979 20272922 PMID: 10813042
LEUKINE maintains viral suppression and extends duration of antiretroviral therapy.
AIDS patient care and STDs (UNITED STATES) Sep 1999, 13 (9) p568-9, ISSN 1087-2914 Journal Code: 9607225
Document type: Clinical Trial; Clinical Trial, Phase III; News; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/16
DIALOG(R)File 155:MEDLINE(R)

10701492 20231310 PMID: 10770541
Phase III study of granulocyte-macrophage colony-stimulating factor in advanced HIV disease: effect on infections, CD4 cell counts and HIV suppression. *Leukine*/HIV Study Group.
Angel J B; High K; Rhame F; Brand D; Whitmore J B; Agosti J M; Gilbert M J; Deresinski S
University of Ottawa, Ontario, Canada.
AIDS (London, England) (ENGLAND) Mar 10 2000, 14 (4) p387-95, ISSN 0269-9370 Journal Code: 8710219
Document type: Clinical Trial; Clinical Trial, Phase III; Controlled Clinical Trial; Journal Article; Randomized Controlled Trial Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
OBJECTIVE: To evaluate the effect of adjuvant granulocyte-macrophage colony-stimulating factor (GM-CSF) (*sargramostim* , yeast-derived recombinant human GM-CSF) on incidence and time to opportunistic infection or death, plasma HIV-RNA, and CD4 cell count in patients with advanced HIV disease. METHODS: This Phase III randomized, double-blind, placebo-controlled trial enrolled subjects with CD4 cell counts < or = 50 x 10(6)/l or < or = 100 x 10(6)/l with a prior AIDS-defining illness on stable antiretroviral therapy. Subjects were stratified by baseline HIV-RNA level (> or = or < 30,000 copies/ml) and randomized to receive subcutaneous injections of GM-CSF 250 microg or placebo three times per week for 24 weeks. Subjects were permitted to continue on blinded drug for up to 20 months. Subjects were evaluated for infections, plasma HIV-RNA, lymphocyte counts, changes in antiretroviral therapy, toxicity, and survival. RESULTS: Three-hundred and nine subjects received at least one dose of study drug, 70% completed 24 weeks of therapy. Groups were well matched at baseline. Significant increases in CD4 cell and neutrophil counts were observed at 1, 3, and 6 months in the GM-CSF group. GM-CSF significantly reduced the incidence of overall infections (78% placebo versus 67% GM-CSF; P = 0.03) and delayed time to first infection (56 days placebo versus 97 days GM-CSF; P = 0.04). No statistical difference in cumulative opportunistic infections was observed between groups; however, among subjects without an opportunistic infection prior to study, the GM-CSF group demonstrated a trend towards fewer subjects with an opportunistic infection on study (26% placebo versus 8% GM-CSF; P = 0.08). Change in HIV-RNA was not significantly different between groups, but significantly fewer GM-CSF subjects with baseline viral load < 30,000 copies/ml had changes in antiretroviral

therapy for increased viral load (42% placebo versus 21% GM-CSF; P = 0.01). In patients with HIV-RNA levels below the limit of detection at baseline, more GM-CSF patients maintained an undetectable viral load at 24 weeks (54% placebo versus 83% GM-CSF; P = 0.02). GM-CSF was well tolerated. CONCLUSIONS: GM-CSF significantly increased CD4 cell count and decreased virological breakthrough and overall infection rate in subjects with advanced HIV disease.

7/3,AB/17
DIALOG(R)File 155:MEDLINE(R)

10647064 20184795 PMID: 10721770
Cost analyses of adjunct colony stimulating factors for acute leukemia: can they improve clinical decision making.
Bennett C L; Stinson T J; Laver J H; Bishop M R; Godwin J E; Tallman M S Chicago VA Healthcare System-Lakeside Division, and Northwestern University, Chicago, IL 60611, USA. cbenne@nwu.edu
Leukemia & lymphoma (SWITZERLAND) Mar 2000, 37 (1-2) p65-70, ISSN 1042-8194 Journal Code: 9007422
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Colony stimulating factors reduce the duration of neutropenia following intensive chemotherapy in a variety of settings, but the advantages in the management of leukemia are inconclusive. The variations in clinical results and the high costs of granulocyte colony-stimulating factor (G-CSF) and granulocyte macrophage colony-stimulating factor (GM-CSF) have led to confusion over appropriate use for leukemia patients. In this paper, we reviewed published information on costs and cost-effectiveness of growth factors for childhood and adult leukemia patients. Medline and Healthstar databases were searched for original research articles that contain cost or cost-effectiveness analyses of G-CSF (filgrastim) and GM-SCF (*sargramostim*) in oncology cooperative group trials. Published manuscripts and abstracts presented at national or international oncology conferences were included. The cost of adjunct treatment was evaluated in two studies of pediatric ALL, one study of adult AML, and two studies of AML in older adults (>55 years). The use of G-CSF for children with ALL was associated with reductions in days to ANC recovery, fewer documented infections, a shorter duration of hospitalization, and small (but not significant) additional costs. In adult AML patients, benefits included a shortening of the duration of neutropenia and hospital stays, a lower incidence of infection and febrile episodes, less use of antibiotics, and cost savings of $2,230 and $2,310 in two studies and an increase if $120 in the third study. This summary suggests that economic analyses can provide useful information to assist clinical decision-making. For pediatric ALL patients, this information indicates that G-CSF use is unlikely to have significant cost implications, and its use should be based on clinical considerations. In studies of adult and older adult AML patients, both GM-CSF and G-CSF have clinical benefits and can be expected to lead to a decrease in overall costs.

7/3,AB/18
DIALOG(R)File 155:MEDLINE(R)

10555853 20090971 PMID: 10623692
Randomized trial of filgrastim, *sargramostim*, or sequential *sargramostim* and filgrastim after myelosuppressive chemotherapy for the harvesting of peripheral-blood stem cells.
Weaver C H; Schulman K A; Wilson-Relyea B; Birch R; West W; Buckner C D Clinical Research Division, Response Oncology, Inc, Memphis, TN, USA. Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Jan 2000, 18 (1) p43-53, ISSN 0732-183X Journal Code: 8309333
Document type: Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: The purpose of this study was to compare the effects of filgrastim, *sargramostim*, or sequential *sargramostim* and filgrastim on CD34(+) cell yields and morbidity after myelosuppressive mobilization chemotherapy (MC). PATIENTS AND METHODS: One hundred fifty-six patients were randomized to receive filgrastim (n = 51), *sargramostim* (n = 52), or *sargramostim* for 5 days followed by filgrastim (n = 53) after MC with either cyclophosphamide and etoposide (n = 75) or paclitaxel and cyclophosphamide (n = 81). RESULTS: Compared with those who received *sargramostim*, patients who received filgrastim had faster recovery of an absolute neutrophil count of 0.5 x 10(9)/L or greater (a median of 11 v 14 days; P =. 0001), with fewer patients requiring RBC transfusions (P =.008), fewer patients with fever (18% v 52%; P = 0.001), fewer hospital admissions (20% v 42%; P =.013), and less intravenous antibiotic therapy (24% v 69%; P =.001). Patients who received filgrastim yielded more CD34(+) cells (median, 7.1 v 2.0 x 10(6)/kg/apheresis; P =.0001), and a higher fraction achieved 2.5 x 10(6) (94% v 78%; P =.021) and 5 x 10(6) (88% v 53%; P =.001) or more CD34(+) cells/kg with fewer aphereses (median, 2 v 3; P =.002) and fewer days of growth-factor treatment (median, 12 v 14; P =.0001). There were no major differences in outcomes between the filgrastim alone and the sequential regimens. After high-dose chemotherapy, patients who had peripheral-blood stem cells (PBSCs) mobilized with

filgrastim or the sequential regimen received higher numbers of CD34(+) cells and had faster platelet recovery (P =.015), with fewer patients (P =.014) receiving fewer platelet transfusions (P =.001) than patients receiving *sargramostim* -mobilized PBSCs. CONCLUSION: It was concluded that filgrastim alone or sequential *sargramostim* and filgrastim were superior to *sargramostim* alone for the mobilization of CD34(+) cells and reduction of toxicities after MC.

7/3,AB/19
DIALOG(R)File 155:MEDLINE(R)

10535488 20078543 PMID: 10613382
Treatment of HIV-related neutropenia.
Wong R J
Amgen Inc., Thousand Oaks, CA 91320, USA.
American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists (UNITED STATES) Dec 15 1999, 56 Suppl 5 pS17-20, ISSN 1079-2082 Journal Code: 9503023 Document type: Journal Article; Review; Review, Tutorial Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Several studies documenting the association of bacteremia and severity of neutropenia in HIV-infected patients, as well as studies using the colony stimulating factors filgrastim or *sargramostim* to prevent and treat neutropenia in this patient population, are summarized. Three studies are described in which low absolute neutrophil count was associated with increased incidence of bacterial infections in patients with HIV infection. Two hematopoietic growth factors called colony stimulating factors (filgrastim and *sargramostim*) are available in the United States, but neither is approved by FDA for the treatment or prevention of neutropenia in HIV-infected patients. Studies have shown both filgrastim and *sargramostim* to be effective in treating neutropenia in HIV-infected patients without increasing the viral load. In one study, filgrastim use on a daily or intermittent basis was associated with reduction in severe neutropenia or death; in addition, filgrastim-treated patients had fewer bacterial infections, fewer hospital days (both total number of days and days associated only with bacterial infections), and a reduced need for i.v. antimicrobials compared with HIV-infected controls. In another study, neutropenia caused by zidovudine was successfully treated with *sargramostim*. Both filgrastim and *sargramostim* show promise in treating and preventing neutropenia in HIV-infected patients. More research is needed to determine the patient population who can best benefit from therapy with these agents and to determine the relative advantages and disadvantages of filgrastim and *sargramostim*.

7/3,AB/20
DIALOG(R)File 155:MEDLINE(R)

10497265 20018254 PMID: 10550137
Granulocyte-macrophage colony-stimulating factor treatment before doxorubicin and cyclophosphamide chemotherapy priming in women with early-stage breast cancer.
Kobrinsky N L; Sjolander D E; Cheang M S; Levitt R; Steen P D MeritCare Roger Maris Cancer Center, Fargo, ND 58122, USA. Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Nov 1999, 17 (11) p3426-30, ISSN 0732-183X Journal Code: 8309333
Erratum in J Clin Oncol 2000 Jan;18(1) 237
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To determine if inhibition of stem-cell activity induced by granulocyte-macrophage colony-stimulating factor ([GM-CSF]; *Sargramostim* ** ; Immunex Corporation, Seattle, WA) withdrawal or priming protects hematopoietic stem cells from the cytotoxic effects of adjuvant chemotherapy for early-stage breast cancer. PATIENTS AND METHODS: Serial blood counts were performed in 20 women with early-stage breast cancer receiving four courses of cyclophosphamide and doxorubicin chemotherapy. By a double-blind, placebo-controlled, balanced randomization, subjects received GM-CSF priming on days 5 to 1 for courses 1 and 3 or courses 2 and 4. RESULTS: Compared with before priming, after priming the times to neutrophil nadir (12.8 +/- 2.5 days v 14.8 +/- 1.5 days, respectively; P =.0001) and platelet nadir (mean +/- SD, 10.1 +/- 1.9 days v 11.1 +/- 2.2 days, P <.05) were shorter, indicating a shift of cytotoxicity to later progenitors. The neutrophil nadir was similar with and without priming (mean +/- SD, 490 +/- 310/microL v 550 +/- 350/microL, respectively; P =.2); however, on day 16 the mean neutrophil count was higher (mean +/- SD, 1030 +/- 580/microL v 690 +/- 370/microL, P =.004), and the proportion of patients with a neutrophil count less than 500/microL was lower after priming than before (six of 35 or 17.1% v 12 of 34 or 35.3%, respectively; P =.04). The platelet nadir was higher (mean +/- SD, 166,000 +/- 51,000/microL after priming v 151,000 +/- 45,000/microL before priming, P =.007), and the duration of thrombocytopenia, ie, a platelet count less than 150,000/microL, was shorter (1.5 +/- 2.1 days v 2.8 +/- 2.9 days, P =.0025) after priming. Episodes of fever and neutropenia were not observed. CONCLUSIONS: GM-CSF priming from days 5 to 1 before doxorubicin and cyclophosphamide chemotherapy was associated with an earlier neutrophil and platelet nadir. On day 16, a higher mean neutrophil count and a lower proportion of

patients with severe (< 500/microL) neutropenia were observed. Beneficial effects on the severity and duration of thrombocytopenia were also noted. These observations support the hypothesis that GM-CSF priming protects hematopoietic progenitors from the cytotoxic effects of chemotherapy.

7/3,AB/21
DIALOG(R)File 155:MEDLINE(R)

10496647 20027058 PMID: 10558962
Granulocyte macrophage colony-stimulating factor as an adjuvant for hepatitis B vaccination of healthy adults.
Hasan M S; Agosti J M; Reynolds K K; Tanzman E; Treanor J J; Evans T G Infectious Diseases Unit, Department of Medicine, University of Rochester School of Medicine and Dentistry, Rochester, New York, USA.
Journal of infectious diseases (UNITED STATES) Dec 1999, 180 (6) p2023-6, ISSN 0022-1899 Journal Code: 0413675
Contract/Grant No.: RR-00044; RR; NCRR
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Granulocyte macrophage colony-stimulating factor (GM-CSF) has shown promise as an adjuvant to improve the kinetics and magnitude of the immune response after vaccination. It was hypothesized that GM-CSF given intramuscularly (IM) with hepatitis B vaccine would result in increased seroconversion rates and antibody titers. In total, 108 healthy volunteers (18-45 years old) received recombinant hepatitis B vaccine IM at 0, 1, and 6 months and were randomized to receive either concurrent GM-CSF (80 or 250 microgram) or placebo IM with the first two vaccinations. The percentages of subjects achieving a protective level of antibody at day 56 were 58.3%, 58.8%, and 58.3% in the placebo and 80- and 250-microgram GM-CSF arms, respectively. The geometric mean titers of antibody measured on days 28, 56, and 189 were not statistically different between arms. GM-CSF given immediately before recombinant hepatitis B vaccination was safe and well tolerated but did not appear to provide significant adjuvant activity at this dose.

7/3,AB/22
DIALOG(R)File 155:MEDLINE(R)

10454524 99446077 PMID: 10516880
Fulminant CNS perivascular lymphocytic proliferation: association with *sargramostim*, a hematopoietic growth factor.
Riggs J E; Mansmann P T; Cook L L; Schochet S S; Hogg J P Department of Neurology, West Virginia University School of Medicine, Morgantown, USA.
Clinical neuropharmacology (UNITED STATES) Sep-Oct 1999, 22 (5) p288-91, ISSN 0362-5664 Journal Code: 7607910
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sargramostim (GM-CSF) therapy was instituted in a 49-year-old woman with hepatitis C on chronic interferon alpha-2b therapy. Within two weeks, she developed progressive confusion, lethargy, and gait disturbance. At autopsy 4 months later, diffuse perivascular nonmonoclonal lymphoid infiltrates were demonstrated throughout the central nervous system (CNS). As the use of hematopoietic growth factors in clinical practice increases, potential adverse effects, such as the fulminant CNS lymphocytic proliferation in this patient, are more likely to be encountered.

7/3,AB/23
DIALOG(R)File 155:MEDLINE(R)

10454067 99446470 PMID: 10518202
Hematopoietic growth factors for chemotherapy-induced neutropenia. Yalcin S
Cancer investigation (UNITED STATES) 1999, 17 (7) p555-6, ISSN 0735-7907 Journal Code: 8307154
Comment on Cancer Invest. 1998;16(6) 366-73; Comment on PMID 9679526 Document type: Comment; Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/24
DIALOG(R)File 155:MEDLINE(R)

10416662 99408826 PMID: 10479132
The safety and efficacy of granulocyte-macrophage colony-stimulating factor (*Sargramostim*) added to indinavir- or ritonavir-based antiretroviral therapy: a randomized double-blind, placebo-controlled trial.
Skowron G; Stein D; Drusano G; Melbourne K; Bilello J; Mikolich D; Rana K ; Agosti J M; Mongillo A; Whitmore J; Gilbert M J
Division of Infectious Diseases, Roger Williams Medical Center, Providence, RI 02908, USA. Gail Skowron@brown.edu
Journal of infectious diseases (UNITED STATES) Oct 1999, 180 (4) p1064-71, ISSN 0022-1899 Journal Code: 0413675
Document type: Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sargramostim is a yeast-derived,

recombinant human granulocyte-macrophage colony-stimulating factor with therapeutic potential in human immunodeficiency virus (HIV) infection. Its safety and activity when used in combination with protease inhibitors were evaluated in a randomized, double-blind trial in which 20 HIV-infected subjects on stable antiretroviral regimens, including indinavir or ritonavir, received *sargramostim* or placebo 3 times a week for 8 weeks. Analysis of HIV virus load excluded any 0. 5 log10 increase due to *sargramostim* (95% confidence interval, -0.68 to 0.44). *Sargramostim* was well tolerated, and inflammatory cytokines and surrogate markers of disease progression, such as serum levels of interleukin-10 and soluble tumor necrosis factor receptors types Iota and IotaIota, remained stable in subjects receiving *sargramostim*. *Sargramostim* treatment was associated with a trend toward decreased HIV RNA (>0.5 log10) and increased CD4+ cell count (>30%). These results became statistically significant only when subjects with baseline virus loads within the limits of detection or baseline CD4 cell count >50 were analyzed. No difference in indinavir pharmacokinetics was observed before or after *sargramostim* therapy.

7/3,AB/25
DIALOG(R)File 155:MEDLINE(R)

10350856 99341877 PMID: 10414911
Hematopoietic growth factor after autologous peripheral blood transplantation: comparison of G-CSF and GM-CSF.
Jansen J; Thompson E M; Hanks S; Greenspan A R; Thompson J M; Dugan M J; Akard L P
Indiana Blood and Marrow Transplantation, Indianapolis 46202, USA. Bone marrow transplantation (ENGLAND) Jun 1999, 23 (12) p1251-6, ISSN 0268-3369 Journal Code: 8702459
Document type: Clinical Trial; Controlled Clinical Trial; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Autologous peripheral blood stem cell (PBSC) transplantation results in rapid hematologic recovery when sufficient numbers of CD34+ cells/kg are infused. Recent studies suggest that filgrastim (G-CSF) administration following transplantation leads to more rapid neutrophil recovery and lower total transplant costs. This study compares the use of G-CSF (5 microg/kg/day) with *sargramostim* (GM-CSF) 500 microg/day from day 0 until neutrophil recovery (ANC >1500/mm3) in patients with breast cancer or myeloma who had PBSC mobilized with the combination of cyclophosphamide, etoposide, and G-CSF. Twenty patients (13 breast cancer and seven myeloma) received GM-CSF and 26 patients (14 breast cancer and 12 myeloma) received G-CSF. The patients were comparable for age and stage of disease, and received stem cell grafts that were not significantly different (CD34+ x 10(6)/kg was 12.5 +/- 11.1 (mean +/- s.d.) for GM-CSF and 19.8 +/- 18.5 for G-CSF; P = 0.10). The use of red cells (2.8 vs 2.3 units), and platelet transfusions (2.5 vs 3.1) was similar for the two groups, as was the use of intravenous antibiotics (4.3 vs 4.6 days) and the number of days with temperature >38.3 degrees C (2.3 vs 1.8). Platelet recovery was also similar in both groups (platelets >50,000/mm3 reached after 11.8 vs 14.9 days). The recovery of neutrophils, however, was faster using G-CSF. ANC >500/mm3 and >1000/mm3 were reached in the GM-CSF group at 10.5 +/- 1.5 and 11.0 +/- 1.7 days, respectively, whereas with G-CSF only 8.8 +/- 1.2 and 8.9 +/- 2.2 days were required (P < 0.001). As a result, patients given G-CSF received fewer injections than the GM-CSF patients (10.9 vs 12.3). Resource utilization immediately attributable to the use of growth factors and the duration of pancytopenia, excluding hospitalization, were similar for the two groups. This study suggests that neutrophil recovery occurs more quickly following autologous PBSC transplant using G-CSF in comparison to GM-CSF, but the difference is not extensive enough to result in lower total cost.

7/3,AB/26
DIALOG(R)File 155:MEDLINE(R)

10276762 99274016 PMID: 10344219
GM-CSF as a systemic adjuvant in a phase II prostate cancer vaccine trial.
Simmons S J; Tjoa B A; Rogers M; Elgamal A; Kenny G M; Ragde H; Troychak M J; Boynton A L; Murphy G P
Cancer Research Division, Pacific Northwest Cancer Foundation, Northwest Hospital, Seattle, Washington 98125, USA.
Prostate (UNITED STATES) Jun 1 1999, 39 (4) p291-7, ISSN 0270-4137 Journal Code: 8101368
Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Recombinant human granulocyte-macrophage colony-stimulating factor (GM-CSF; *Leukine* [*sargramostim*], Immunex Corp., Seattle, WA) was administered to a subgroup of 44 patients in a phase II clinical trial for prostate cancer using DC pulsed with HLA-A2-specific prostate-specific membrane antigen (PSMA) peptides. Our purpose was to determine if GM-CSF caused any enhancement of patients' immune responses, including enhancement of clinical response to the DC-peptide treatment. This report compares the clinical responses to DC-peptide infusions with and without systemic GM-CSF treatment. METHODS: GM-CSF was administered by subcutaneous injection at a dose of 75 microg/m2/day for 7 days with each of six infusion

cycles. Prefilled syringes were supplied to the patients for self-administration. RESULTS: One complete and 8 partial responders were identified among 44 patients who received GM-CSF, as compared to 2 complete and 17 partial responders among 51 patients who did not receive GM-CSF. For patients who received GM-CSF and were tested by delayed-type hypersensitivity (DTH) skin test, 3 cases of improved immune response were identified, compared to 5 cases of improvement in patients who did not receive GM-CSF. The main GM-CSF side effects reported were local reactions at the site of injection, fatigue, pain, and fever. Most reported side effects were of mild severity, with some cases of moderate severity leading to discontinuation of GM-CSF. CONCLUSIONS: Our results suggest GM-CSF as employed in this trial did not detectably enhance clinical response to DC-peptide infusions, or significantly enhance the measured immune response.

7/3,AB/27
DIALOG(R)File 155:MEDLINE(R)

10081869 99061765 PMID: 9845514
Emerging applications of recombinant human granulocyte-macrophage colony-stimulating factor.
Armitage J O
Department of Internal Medicine, University of Nebraska Medical Center, Omaha, NE, USA.
Blood (UNITED STATES) Dec 15 1998, 92 (12) p4491-508, ISSN 0006-4971 Journal Code: 7603509
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/28
DIALOG(R)File 155:MEDLINE(R)

10047495 99035512 PMID: 9815298
Sequential phase II trials of fluorouracil and interferon beta ser with or without *sargramostim* in patients with advanced colorectal carcinoma.
Wadler S; Haynes H; Rozenblit A; Hu X; Kaleya R; Wiernik P H Department of Oncology, Montefiore Medical Center, Bronx, New York 10467, USA.
cancer journal from Scientific American (UNITED STATES) Sep-Oct 1998, 4 (5) p331-7, ISSN 1081-4442 Journal Code: 9513568
Contract/Grant No.: CA13330; CA; NCI
Document type: Clinical Trial; Clinical Trial, Phase II; Controlled Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Preclinical and early clinical trials suggested that the biologic agent interferon beta ser (IFN beta ser) may augment the anticancer activity of 5-fluorouracil (5-FU). The current studies were undertaken to explore the optimal schedule of IFN beta ser and to determine whether the hematopoietic growth factor *sargramostim* (granulocyte-macrophage colony-stimulating factor) could reduce the hematologic and gastrointestinal toxicities of the chemotherapy. METHODS: Three sequential, single-institution phase II trials using different regimens were initiated. Patients were required to have advanced, histologically documented colorectal carcinoma with no prior chemotherapy; to have adequate bone marrow, renal, and hepatic function; to be fully ambulatory; and to give informed consent. All patients received 5-FU, 750 mg/m2 intravenously as an infusion daily for 5 days, followed by 5-FU, 750 mg/m2, as an intravenous bolus every week beginning day 15. Patients in arm A received IFN beta ser, 9 MU subcutaneously, three times a week. Patients in arm B received IFN beta ser, 9 MU subcutaneously every day. Patients in arm C were treated exactly as in arm B but also received *sargramostim* , 250 micrograms subcutaneously on days they did not receive 5-FU. Beginning day 15, all patients received IFN beta ser exactly 10 minutes before receiving the 5-FU bolus. RESULTS: There were 81 patients enrolled: 19 in arm A; 40 in arm B; and 22 in arm C. Myelosuppression and diarrhea were the most common toxicities. Increasing the frequency of IFN beta ser administration in arm B resulted in a doubling of the rate of diarrhea from 11% to 22%, and the addition of *sargramostim* in arm C failed to reduce this. *Sargramostim* did reduce the incidence of grade 3 to 4 leukopenia, but this did not allow intensification of dosing or result in improved response or survival among patients in arm C. IFN-mediated fatigue was also common, occurring in 37% to 43% of patients. Patients receiving IFN beta ser on the intermittent schedule tolerated full-dose therapy longer than those on the daily schedule (10 weeks versus 5 weeks, $P < 0.01$). The response rates in the three arms were 21%, 35%, and 27%; there was no difference in median survival (15 months for all three arms). CONCLUSIONS: The combination of 5-FU and IFN beta ser was active in patients with advanced colorectal carcinoma, and survival with this regimen was comparable to or better than that with other modulating regimens. The intermittent schedule of IFN beta ser was better tolerated than than the daily schedule.

7/3,AB/29
DIALOG(R)File 155:MEDLINE(R)

10028617 98703779 PMID: 11365393
Looking down the drug pipeline.
Cadman J
GMHC treatment issues : the Gay Men's Health Crisis newsletter of experimental AIDS therapies

(UNITED STATES) Mar 1998, 12 (3) p5-9, ISSN 1077-1824 Journal Code: 9509489
Document type: Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed

Reports at the 5th Conference on Retroviruses and Opportunistic Infections addressed new anti-HIV agents in primary phases of development that offer treatment alternatives to people with little or no treatment history and individuals with few treatment choices. FTC, a new nucleoside analog produced by Triangle Pharmaceuticals, is an alternative to 3TC. F-ddA (lodenosine), a nucleoside analog licensed by US Bioscience, is structurally similar to ddI and is reported to have good bioavailability, once-a-day dosing, and no bone marrow suppression. F-ddA has also shown in vitro activity against multidrug-resistant strains of HIV. Adult and pediatric studies are currently being conducted by the National Cancer Institute (NCI) and US Bioscience. Oral versus IV PMPA shows promising results as a possible alternative for 3TC- and AZT-experienced patients. Further testing is being done by Gilead Sciences and HIV Network for Prevention Trials (HIVNET). Abbott Laboratories is developing a second-generation protease inhibitor, ABT-378, which has a ten-fold greater antiviral activity in vitro than the original, ritonavir. It is administered with ritonavir to increase ABT-378 levels in the blood, but has no food requirements, and less severe side effects. Two trials are being conducted: one for patients who are treatment-naive and the second for patients who are failing other protease inhibitors. Immune-based therapies, such as *Leukine* (GM-CSF), are used to handle neutropenia and offset bone marrow toxicities from drugs. Concerns that GM-CSF may increase viral replication may be balanced by using highly active antiretroviral therapy. FP-21399, developed by Lexigen Pharmaceuticals, is being tested as an HIV fusion inhibitor.

7/3,AB/30
DIALOG(R)File 155:MEDLINE(R)

10028434 98703558 PMID: 11365210
A view of the future: Dr. Mark Gilbert of Immunex talks about immune based therapy. Interview by Robert Nielsen.
Gilbert M
STEP perspective (UNITED STATES) Winter 1998, 98 (1) p15-7, Journal Code: 9888939
Document type: Interview; Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed

Dr. Mark Gilbert, Medical Director of the biopharmaceutical company Immunex, explains that Highly Active Antiretroviral Therapy (HAART) has provided a foundation to begin addressing the effects of therapy on the immune system. Immunex is focusing on the role that *Leukine*, a recombinant, yeast-derived GM-CSF, has on both advanced AIDS and the early onset of HIV. A Phase III trial is evaluating whether *Leukine* can reduce the incidence of opportunistic infections and death in 300 people with AIDS. Dr. Gilbert discusses the importance of the thymus for T cell development and its effect on immune system functions. Immunex is searching for a method to either maintain or to restore the immune system. Restoring the thymus may restore host immunity; however, very little is known about the thymus. According to Gilbert, the most promising idea for restoring immune function is intermittent low-dose interleukin-2 (IL-2). HIV-positive individuals using HAART therapy should consider talking to a health care provider about immune modulation therapy.

7/3,AB/31
DIALOG(R)File 155:MEDLINE(R)

09911837 98344469 PMID: 9679526
A comparison of efficacy of *sargramostim* (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in the therapeutic setting of chemotherapy-induced myelosuppression.
Beveridge R A; Miller J A; Kales A N; Binder R A; Robert N J; Harvey J H; Windsor K; Gore I; Cantrell J; Thompson K A; Taylor W R; Barnes H M; Schiff S A; Shields J A; Cambareri R J; Butler T P; Meister R J; Feigert J M; Norgard M J; Moraes M A; Helvie W W; Patton G A; Mundy L J; Henry D; Sheridan M J; et al
Fairfax Hematology-Oncology Associates, Inc., Annandale, Virginia, USA. Cancer investigation (UNITED STATES) 1998, 16 (6) p366-73, ISSN 0735-7907 Journal Code: 8307154
Comment in Cancer Invest. 1999;17(7) 555-6; Comment in PMID 10518202 Document type: Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A randomized, double-blind, multicenter study in 181 afebrile cancer patients with ANC levels < 500/microL receiving myelosuppressive chemotherapy was undertaken to compare *sargramostim* (yeast-derived recombinant human granulocyte-macrophage colony-stimulating factor, RhuGM-CSF) and filgrastim (bacteria-derived recombinant human granulocyte colony-stimulating factor, RhuG-CSF) in the treatment of chemotherapy-induced myelosuppression. Patients

received daily subcutaneous (SC) injections of either agent until ANC levels reached at least 1500/microL. There was no statistical difference between treatment groups in the mean number of days to reach an ANC of 500/microL, but the mean number of days to reach ANC levels of 1000/microL and 1500/microL was approximately one day less in patients receiving filgrastim. Fewer patients in the *sargramostim* arm were hospitalized, and they had a shorter mean length of hospitalization, mean duration of fever, and mean duration of i.v. antibiotic therapy compared with patients who received filgrastim. Both growth factors were well tolerated. No patient was readmitted to the hospital after growth factor was discontinued. *Sargramostim* and filgrastim have comparable efficacy and tolerability in the treatment of standard-dose chemotherapy-induced myelosuppression in community practice.

7/3,AB/32
DIALOG(R)File 155:MEDLINE(R)

09735561 98167629 PMID: 9508204
Randomized, placebo-controlled, multicenter trial of granulocyte-macropha ge colony-stimulating factor as infection prophylaxis in oncologic surgery. *Leukine* Surgical Prophylaxis Research Group.
Meropol N J; Wood D E; Nemunaitis J; Petrelli N J; Lipman B J; Agosti J M ; Whitmore J B
Division of Medicine, Roswell Park Cancer Institute, Buffalo, NY 14263, USA. meropol@sc3101.med.buffalo.edu
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Mar 1998, 16 (3) p1167-73, ISSN 0732-183X Journal Code: 8309333
Document type: Clinical Trial; Clinical Trial, Phase III; Journal Article ; Multicenter Study; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: Postoperative infections are a frequent source of preventable morbidity and mortality in the oncologic population. Granulocyte-macrophage colony-stimulating factor (GM-CSF) is a potent modulator of immune effector cells in vitro and in vivo. This study was conducted to determine whether GM-CSF, when administered perioperatively, could reduce the incidence of surgical infections in cancer patients. METHODS: This was a prospective, randomized, placebo-controlled, multicenter study. Cancer patients at high risk of infectious surgical morbidity were randomized to receive GM-CSF 125 microg/m2 per day or placebo subcutaneously for 8 days beginning 3 days preoperatively. Routine antibiotic prophylaxis was administered to all patients. RESULTS: Three hundred ninety-nine patients were enrolled, with 198 randomized to receive GM-CSF. Twenty-one percent of patients experienced infections during the first 2 weeks postoperatively, and there was no difference in infection rate between the study groups. The most common sites of infection were respiratory tract (53%) and surgical wound (25%). The duration of operation and American Society of Anesthesiology (ASA) physical status classification were the most significant predictors of infection in multivariate analysis. GM-CSF was well tolerated and was not associated with fever. CONCLUSION: The eligibility criteria for this study were successful at defining a patient subgroup at high risk for postoperative infections. At an immunomodulatory dose of 125 microg/m2 per day, GM-CSF was safe and well tolerated, but did not reduce the incidence of postoperative infections in this high-risk oncologic population. Infectious morbidity in surgical oncology remains an important subject for continued clinical investigation.

7/3,AB/33
DIALOG(R)File 155:MEDLINE(R)

09653647 98082934 PMID: 9422471
High-dose chemotherapy with autologous peripheral blood progenitor cell support for primary breast cancer in patients with 4-9 involved axillary lymph nodes.
Bearman S I; Overmoyer B A; Bolwell B J; Taylor C W; Shpall E J; Cagnoni P J; Mechling B E; Ronk B; Baron A E; Purdy M H; Ross M; Jones R B Bone Marrow Transplant Programs of University of Colorado Health Sciences Center, Denver 80262, USA.
Bone marrow transplantation (ENGLAND) Dec 1997, 20 (11) p931-7, ISSN 0268-3369 Journal Code: 8702459
Contract/Grant No.: CA 61508; CA; NCI; CA 61532; CA; NCI Document type: Clinical Trial; Journal Article; Multicenter Study Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Breast cancer patients with more than three involved axillary lymph have a high likelihood of relapse after adjuvant therapy. Early results of administration of high-dose chemotherapy (HDCT) and autologous peripheral blood progenitor cells (PBPC) to patients with primary breast cancer and > or = 10 involved axillary nodes have been encouraging. We performed a multicenter trial to determine whether HDCT could be safely administered to patients with primary breast cancer involving 4-9 axillary lymph nodes. Fifty-four patients with stage II or III breast cancer and 4-9 involved axillary lymph nodes received doxorubicin-based induction chemotherapy, followed by high-dose cyclophosphamide (5.625 g/m2), cisplatin (165 mg/m2), and BCNU (450 mg/m2) and PBPC mobilized by *sargramostim* (GM-CSF) or filgrastim (G-CSF). After completion of HDCT, patients received radiation therapy to the chest wall or involved breast, plus tamoxifen.

Survival and disease-free survival, time to engraftment, and charges associated with HDCT were determined. Plasma concentrations of BCNU were determined and plasma AUC(BCNU) was calculated. Fifty-four patients were evaluable for survival and relapse-free survival. Fifty-two patients received HDCT with PBPC support and were evaluable for toxicity. Fifteen patients (29%) developed late pulmonary drug toxicity, which resolved with a 10-week course of corticosteroids in all but one affected patient, who subsequently died of pulmonary toxicity. Ten patients relapsed a median of 426 days (range 86-1117 days) after the start of induction chemotherapy, seven of whom have died. Forty-three patients are alive and breast cancer-free at a median of 947 days (range 661-1730 days) after the start of therapy, including one patient who developed myelodysplastic syndrome 809 days after the start of HDCT. Actuarial 4-year survival and disease-free survival from the start of treatment are 84 and 71%, respectively. Mean plasma AUC(BCNU) was 400 (range 82-1255) microgxmin/ml and was not statistically different from that measured in historical controls who received 600 mg/m2 of BCNU. Combined hospital and physician charges for patients treated at the University of Colorado decreased from a mean of $125845 for the first four patients to $77126 for the final seven patients. We conclude that HDCT with autologous PBPC can be administered with acceptable safety to patients with primary breast cancer involving 4-9 axillary lymph nodes. An ongoing, prospective randomized trial is evaluating the efficacy of HDCT for this patient group.

7/3,AB/34
DIALOG(R)File 155:MEDLINE(R)

09611907 98039314 PMID: 9372045
American Society of Clinical Oncology guidelines for the use of hematopoietic colony-stimulating factors.
Ozer H
Winship Cancer Center, Emory University School of Medicine, Atlanta, GA 30322, USA.
Current opinion in hematology (UNITED STATES) Jan 1996, 3 (1) p3-10, ISSN 1065-6251 Journal Code: 9430802
Document type: Guideline; Journal Article; Practice Guideline Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The hematopoietic colony-stimulating factors have been introduced into clinical practice as additional supportive measures that can reduce the likelihood of neutropenic complications due to chemotherapy. Clinical benefit has been shown, but the high cost of colony-stimulating factors has led to concern about their appropriate use. The American Society of Clinical Oncology has established evidence-based, clinical practice guidelines for the use of colony-stimulating factors in patients who are not enrolled in clinical trials. An expert multidisciplinary panel reviewed the clinical data documenting the activity of colony-stimulating factors. For each common clinical situation, the panel formulated a guideline to encourage reasonable use of colony-stimulating factors to preserve effectiveness but discourage excess use when little marginal benefit is anticipated. Outcomes considered in evaluating colony stimulating factor benefit included duration of neutropenia, incidence of febrile neutropenia, incidence and duration of antibiotic use, frequency and duration of hospitalization, infectious mortality, chemotherapy dose intensity, chemotherapy efficacy, quality of life, colony-stimulating factor toxicity, and economic impact. To the extent that these data were available, the panel placed greatest value on survival benefit, reduction in rates of febrile neutropenia, decreased hospitalization, and reduced costs. Lesser value was placed on alterations in absolute neutrophil counts.

7/3,AB/35
DIALOG(R)File 155:MEDLINE(R)

09585165 98025635 PMID: 9377627
Neutropenia and neoplasia: an overview of the pharmacoeconomics of *sargramostim* in cancer therapy.
Desch C E; Ozer H
Massey Cancer Center, Richmond, Virginia, USA.
Clinical therapeutics (UNITED STATES) Jul-Aug 1997, 19 (4) p847-65, ISSN 0149-2918 Journal Code: 7706726
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Sargramostim is a myeloid growth factor that is widely used as adjunctive support in patients with neutropenia. *Sargramostim* enhances neutrophil recovery and myeloid engraftment, reduces infectious complications, and shortens the duration of hospitalization in selected patients. The high cost of *sargramostim* and other myeloid growth factors and their ability to reduce infections and days of hospitalization have generated interest in their pharmacoeconomic impact. Cost minimization studies in patients receiving chemotherapy for acute myelogenous leukemia and in recipients of autologous bone marrow transplantation (BMT) show estimated cost savings with *sargramostim* of 1996 US$12,513 and 1994 US$14,500, respectively. These data are consistent with cost savings of 1989 US$16,000 using molgramostim in autologous BMT recipients. Although no pharmacoeconomic data have been published in patients with other conditions, clinical outcomes research demonstrates a clear benefit for *sargramostim* administration in recipients of

peripheral blood progenitor cell and allogeneic BMT and in patients who experience graft delay or failure. Because of reductions in the duration of hospitalization and infectious complications, economic outcomes of these conditions would probably also support *sargramostim* use. More data regarding the use of *sargramostim* for chemotherapy-induced neutropenia are required to properly assess the pharmacoeconomic impact in these patients.

7/3,AB/36
DIALOG(R)File 155:MEDLINE(R)

09578108 97702863 PMID: 11364571
Study of GM-CSF enrolling.
PI perspective (UNITED STATES) Jul 1997, (No 22) p14, ISSN 1058-7454 Journal Code: 9102818
Document type: Newspaper Article
Languages: ENGLISH
Main Citation Owner: NLM
Abstract Source: AIDS
Record type: Completed
A study to determine if GM-CSF (*Leukine*), in addition to standard therapies, will delay HIV disease progression and death by enhancing immune function is in clinical trials around the United States. Participants can be on any standard anti-HIV and anti-opportunistic infection regimens. A phone number is provided for further information.

7/3,AB/37
DIALOG(R)File 155:MEDLINE(R)

09514043 97401669 PMID: 9257425
Randomized trial comparing the tolerability of *sargramostim* (yeast-derived RhuGM-CSF) and filgrastim (bacteria-derived RhuG-CSF) in cancer patients receiving myelosuppressive chemotherapy.
Beveridge R A; Miller J A; Kales A N; Binder R A; Robert N J; Heisrath-Evans J; Koczyk-Scripka K; Pashko S; Norgard M J; Barnes H M; Taylor W R; Thompson K A; Smith L F; Ueno W M; Dobrzynski R F; Warren R D; Katcher D; Byrne P J; Dunning D M; Winokur S H; Lockey J L; Cambareri R J; Butler T P; Meister R J; Fiegert J M
Fairfax-Prince William Hematology Oncology Associates, Annandale, VA 22003-1296, USA.
Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer (GERMANY) Jul 1997, 5 (4) p289-98, ISSN 0941-4355 Journal Code: 9302957
Document type: Clinical Trial; Journal Article; Multicenter Study; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A prospective, randomized, double-blind, multicenter study in cancer patients receiving myelosuppressive chemotherapy was undertaken to evaluate and compare the tolerability of *sargramostim* (yeast-derived recombinant human granulocyte-macrophage colony-stimulating factor, RhuGM-CSF) and filgrastim (bacteria-derived recombinant human granulocyte colony-stimulating factor, RhuG-CSF) in the prophylaxis or treatment of chemotherapy-induced neutropenia. In all, 137 evaluable patients received *sargramostim* (300 micrograms; 193 mg/m2) or filgrastim (481 mg; 7 mg/kg) once daily by self-administered s.c. injection, usually beginning within 48 h after completion of chemotherapy. With the exception of a slightly higher incidence of grade 1 fever (< 38.1 degrees C) with *sargramostim* , there were no statistically significant differences in the incidence or severity of local or systemic adverse events possibly related to the growth factors. Although the study was not designed to evaluate efficacy directly, there also were no statistically significant differences between treatment groups in total days of growth factor therapy, days of hospitalization, or days of i.v. antibiotic therapy during the treatment period. Both *sargramostim* and filgrastim were comparably well tolerated when given by s.c. injection in this group of patients, and no clinically significant differences between the growth factors were demonstrated.

7/3,AB/38
DIALOG(R)File 155:MEDLINE(R)

09184291 97071272 PMID: 8914197
Development and shelf-life determination of recombinant human granulocyte--macrophage colony-stimulating factor (*LEUKINE*, GM-CSF).
Geigert J; Ghrist F D
IDEC Pharmaceuticals Corporation, San Diego, California 92121, USA. Pharmaceutical biotechnology (UNITED STATES) 1996, 9 p329-42, ISSN 1078-0467 Journal Code: 9310302
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/39
DIALOG(R)File 155:MEDLINE(R)

09166394 97076178 PMID: 8918495
Randomized double-blind prospective trial to evaluate the effects of *sargramostim* versus placebo in a moderate-dose fluorouracil, doxorubicin, and cyclophosphamide adjuvant chemotherapy program for stage II and III breast cancer.
Jones S E; Schottstaedt M W; Duncan L A; Kirby R L; Good R H; Mennel R G; George T K; Snyder D A; Watkins

D L; Denham C A; Hoyes F A; Rubin A S Texas Oncology, PA, Dallas 75246, USA.
Journal of clinical oncology : official journal of the American Society of Clinical Oncology (UNITED STATES) Nov 1996, 14 (11) p2976-83, ISSN 0732-183X Journal Code: 8309333
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To determine the effects of *sargramostim* (recombinant human granulocyte-macrophage colony-stimulating factor [rhu GM-CSF]) on the incidence, duration, and complications of myelosuppression after moderate-dose fluorouracil, doxorubicin, cyclophosphamide (FAC) adjuvant chemotherapy in patients with node-positive breast cancer. PATIENTS AND METHODS: In this randomized, double-blind, placebo-controlled study, 142 women with stage II and III breast cancer were to receive four 21-day cycles of chemotherapy that consisted of fluorouracil 600 mg/m2 intravenously (IV), doxorubicin 60 mg/m2 IV, and cyclophosphamide 750 mg/m2 IV on day 1, followed by placebo or GM-CSF 250 micrograms/m2/d daily subcutaneously (SC) on days 3 through 15. All patients received prophylactic ciprofloxacin by mouth when the absolute neutrophil count (ANC) was less than 1,000/microL. RESULTS: Eighty-six percent of GM-CSF patients (n = 62) and 96% of placebo patients (n = 69) completed four assessable cycles of treatment on study. Overall, the median duration of severe neutropenia (ANC < 500/microL) was 2.8 days with GM-CSF and 6.8 days with placebo (P < .001); the duration of ANC less than 1,000/microL was 6.0 versus 9.1 days, respectively (P < .001). Hospitalizations for febrile neutropenia were uncommon in either group: GM-CSF, six; placebo, eight. The only other difference in hematologic toxicity was grade 3/4 thrombocytopenia observed with greater frequency in GM-CSF patients than placebo patients in cycles 3 and 4. GM-CSF increased mean the FAC dose-intensity among patients who completed two or more cycles (P < .001). GM-CSF was generally well tolerated and associated with more injection-site reactions, but less mucositis than placebo. There were no deaths on study. CONCLUSION: GM-CSF significantly enhanced ANC recovery after FAC chemotherapy; it decreased the incidence and duration of associated neutropenia and moderately increased the dose-intensity of adjuvant chemotherapy. Whether these effects will ultimately translate into improved long-term outcome remains to be determined.

7/3,AB/40
DIALOG(R)File 155:MEDLINE(R)

09068523 96428893 PMID: 8831995
Antitumor and accessory immune activities of peripheral blood stem cells mobilized with granulocyte-macrophage colony-stimulating factor. Triozzi P L; Tucker F; Benzies T; Balcerzak S P
Ohio State University Comprehensive Cancer Center, Arthur G James Cancer Hospital and Research Institute, Columbus, USA.
Bone marrow transplantation (ENGLAND) Jul 1996, 18 (1) p47-52, ISSN 0268-3369 Journal Code: 8702459
Contract/Grant No.: 2P30CA16508; CA; NCI; N01-CM-47666-01; CM; NCI Document type: Clinical Trial; Clinical Trial, Phase I; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The characteristics of PBSC mobilized with GM-CSF, which has been shown to augment monocyte/macrophage (Mo/Mx) antitumor and accessory activities, were evaluated. Patients with metastatic cancers were treated with GM-CSF at 5 micrograms/kg sc, days 1 to 7; leukaphereses were performed on days 6 and 7. A mean of 3.3 x 10(10) mononuclear cells were collected, 59% of which were lymphoid and 32%, monocytoid. Spontaneous Mo/Mx tumor cell cytotoxicity was not detectable in the leukapheresis product, either before or after cryopreservation; Mo/Mx tumor cell cytotoxicity, however, was inducible in vitro with IFN-gamma. Likewise, spontaneous lymphocyte cytotoxicity was not detectable in the leukapheresis product; lymphokine-activated killer cell activity was inducible in vitro with IL-2. Whereas lymphoproliferative responses to tetanus toxoid of cryopreserved PBSC were less than that of freshly collected PBSC, the capacity of Mo/Mx from cryopreserved PBSC to function as accessory cells in the lymphoproliferative response was maintained. These results indicate that significant numbers of immune cells can be mobilized with GM-CSF alone. Cryopreserved, GM-CSF-mobilized PBSC do not demonstrate spontaneous antitumor cytolytic activity; however, accessory activity is present and antitumor cytolytic activity mediated by both monocytoid and lymphoid cells is inducible.

7/3,AB/41
DIALOG(R)File 155:MEDLINE(R)

09066033 96424008 PMID: 8826608
A randomized phase I study of oral etoposide with or without granulocyte-macrophage colony-stimulating factor for the treatment of patients with advanced cancer.
Weiss G R; Shaffer D W; DeMoor C; Rinaldi D A; Rodriguez G I; Eckardt J R ; Stephens C; Von Hoff D D
Division of Medical Oncology, University of Texas Health Science Center at San Antonio 78284, USA.
Anti-cancer drugs (ENGLAND) Jun 1996, 7 (4)

p402-9, ISSN 0959-4973 Journal Code: 9100823
Document type: Clinical Trial; Clinical Trial, Phase I; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The purpose of this study was to evaluate the feasibility of chronic oral administration of etoposide with granulocyte-macrophage colony-stimulating factor (GM-CSF) [*sargramostim* (Immunex)] coadministration or premedication; to estimate and compare the frequency of toxicities accompanying etoposide administration alone, etoposide/GM-CSF coadministration and etoposide with GM-CSF premedication. Thirty-nine patients with advanced treatment-refractory malignancies were enrolled to this study. Eligible patients were randomized to one of three treatment arms: daily oral etoposide alone for 21 days (arm A); daily oral etoposide for 21 days with GM-CSF, 250 micrograms/m2, s.c. twice daily for the first 10 days of etoposide administration (arm B); or daily oral etoposide for 21 days with GM-CSF twice daily for the sixth through second days preceding etoposide administration (arm C). Courses of treatment were repeated every 28 days. Etoposide dosages for each arm were 25, 50, 75 and 100 mg/m2/day. At least three patients were treated at each dosage level until dose-limiting toxicity was observed. Patients had twice weekly blood counts and weekly clinical examinations to assess toxicity. Patients with measurable or evaluable evidence of cancer were assessed for antitumor response after every other course of therapy. Nadir neutrophil counts at each dosage level were compared between treatment arms by non-parametric Wilcoxen rank sum tests. GM-CSF coadministration (arm B) or premedication (arm C) with daily chronic oral etoposide was feasible and did not lead to excessive hematological toxicity. Pairwise comparisons of neutrophil nadirs for the first course of therapy for each treatment arm did not demonstrate any significant differences and, at most, a slight trend favoring improved neutrophil nadirs was shown for arm C compared to arm A ($p = 0.07$). Dose intensity as measured by mean days of etoposide administered per patient for each arm suggested only slight improvement in etoposide tolerance for treatment arms B and C. The conclusion, GM-CSF can be safely administered to patients receiving chronic daily oral etoposide. It appears that GM-CSF provides no clinically useful improvement in granulocyte tolerance of therapy.

7/3,AB/42
DIALOG(R)File 155:MEDLINE(R)

08971338 96336761 PMID: 8726588
The emergence of peripheral blood progenitor cells to support intensive chemotherapy for patients with breast cancer.
Demetri G D
Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, Massachusetts 02115, USA.
Pharmacotherapy (UNITED STATES) May-Jun 1996, 16 (3 Pt 2) p94S-100S, ISSN 0277-0008 Journal Code: 8111305
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Increasing evidence supports the hypothesis that "dose" is critical to the clinical outcomes of cytotoxic chemotherapy for patients with breast cancer. Clinical trials continue to investigate whether higher doses of chemotherapy lead to proportionate improvements in the outcomes of patients. Delivery of dose-intensive chemotherapy has been facilitated by technological advancements in supportive care. Improved antiemetics have led to increased patient tolerance of the most acute symptoms of aggressive chemotherapeutic dosing. Chemotherapy-induced myelosuppression may be minimized in a lineage-specific manner by appropriate use of hematopoietic cytokines such as filgrastim (granulocyte colony-stimulating factor), *sargramostim* (granulocyte-macrophage colony-stimulating factor), and/or epoetin alfa (erythropoietin). However, cumulative myelotoxicity occurs with dose-intensive chemotherapy over multiple cycles despite adjunctive cytokine support. Additionally, no cytokine has yet been demonstrated to support platelet production to any clinically significant degree although several regulators of platelet production (such as thrombopoietin, IL-6, and IL-11) are in clinical trials. Many cytokines can induce the mobilization of hematopoietic progenitor and stem cells from the bone marrow into the circulating blood pool, where these cells may be harvested. Clinical use of these cytokine-mobilized peripheral blood progenitor cells (also known as PBPCs or, commonly, as blood stem cells) has documented the effectiveness of these cells to reconstitute multilineage blood production following very high-dose chemotherapy. The ease with which PBPCs can be collected and their reproducible clinical effectiveness to support patients through intensive treatment protocols have led to a virtual elimination of bone marrow as the source of cellular support for myeloablative chemotherapy in many transplant centers. Novel investigative approaches are also possible with PBPCs. In this review, the historical background of PBPCs is summarized, and the potential benefits (including economic advantages) of PBPCs to support dose-intensive chemotherapy for treating breast cancer are discussed. While dose intensification of breast cancer chemotherapy to the degree requiring PBPC support remains controversial and, in most centers, investigational, there is no doubt that PBPCs are an effective adjunct to the hematopoietic support of patients undergoing transplant-level

cytotoxic treatments. Further study will undoubtedly lead to increased use of PBPCs in novel treatments for patients with breast cancer and other solid tumors.

7/3,AB/43
DIALOG(R)File 155:MEDLINE(R)

08904009 96264758 PMID: 8673688
Immediate hypersensitivity to human recombinant granulocyte-macrophage colony-stimulating factor associated with a positive prick skin test reaction.
Engler R J; Weiss R B
Allergy-Immunology Service, Department of Medicine, Walter Reed Army Medical Center, Washington, DC, USA.
Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology (UNITED STATES) Jun 1996, 76 (6) p531-4, ISSN 1081-1206 Journal Code: 9503580
Contract/Grant No.: CA26806; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Recombinant human granulocyte-macrophage colony-stimulating factor (rhu GM-CSF), also known as *sargramostim* , is used to accelerate myeloid recovery following bone marrow transplantation or cytotoxic chemotherapy. "Anaphylactic" reactions to *sargramostim* have been reported on a limited basis and are poorly characterized. OBJECTIVE: It is the purpose of this report to describe an adverse reaction to *sargramostim* treatment involving palmar itching, urticaria, angioedema, and throat tightness and to demonstrate the utility of prick skin testing to determine type I sensitization. METHODS: Prick skin testing with 100 and 250 micrograms/mL *sargramostim* and 300 micrograms/mL rhu G-CSF (filgrastim) was performed in the patient and four control subjects. RESULTS: The patient experienced an immediate wheal and flare reaction with both concentrations of *sargramostim* while the control subjects demonstrated no reaction. There was also no reaction with filgrastim (rhu G-CSF) in either group and the patient subsequently tolerated filgrastim therapy. CONCLUSION: Prick skin testing with rhu GM-CSF and rhu G-CSF may be useful to demonstrate type I sensitization. Additional studies are needed to determine the incidence and prevalence of skin test reactions in larger numbers of patients with cytokine therapy exposure.

7/3,AB/44
DIALOG(R)File 155:MEDLINE(R)

08895786 96266921 PMID: 8646722
Phase II clinical trial with 5-fluorouracil, recombinant interferon-alpha-2b, and cisplatin for patients with metastatic or regionally advanced carcinoma of the esophagus.
Wadler S; Haynes H; Beitler J J; Hu X; Fell S; Camacho M; Levine B; Wiernik P H
Albert Einstein Cancer Center, Bronx, New York 10467, USA. Cancer (UNITED STATES) Jul 1 1996, 78 (1) p30-4, ISSN 0008-543X Journal Code: 0374236
Contract/Grant No.: CA 13330; CA; NCI
Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
BACKGROUND: Recombinant interferon-alpha (IFN) augments the cytotoxicity of both 5-fluorouracil (5-FU) and cisplatin in vitro. A phase II study of 5-FU and IFN resulted in response rates of 25-27% in patients with metastatic esophageal carcinoma. METHODS: A Phase II trial was initiated to determine the clinical utility of a three-drug combination (FIP) in patients with regionally advanced or metastatic esophageal carcinoma. Eligibility included biopsy-proven Stage III or IV squamous cell carcinoma or adenocarcinoma of the esophagus with no prior chemotherapy, adequate performance status, nutritional status, bone marrow, hepatic and renal function, and signed informed consent. Patients were treated in the exact sequence of IFN==>cisplatin==>5-FU. Patients received 5-FU, 750 mg/m2/day for 5 days followed by weekly bolus therapy at the same dose; cisplatin, 100 mg/m2 on Day 1, followed by weekly therapy, 25 mg/m2 over the course of 1 hour; and IFN, 10 MU subcutaneously 3 times/week beginning on Day 1. All patients received *sargramostim* (granulocyte-macrophage colony-stimula ting factor, Escherichia coli-derived), 5 micrograms/kg subcutaneously 5 times/week. No patients received radiotherapy. RESULTS: Twenty-four patients were enrolled; 23 were eligible, and 1 was excluded on pathology review (patient was found to have a leiomyoblastoma). The demographics of the population were: median age, 63 years (range, 43-73 years); 18 male patients; squamous cell carcinoma: adenocarcinoma ratio, 22:1, and Stage III:IV ratio, 10:13. Grade 3-4 National Cancer Institute Common Toxicity Criteria toxicities included: leukopenia (13), thrombocytopenia (14), and infection (9). Grade 3 diarrhea, mucositis, and vomiting occurred in 6 patients, 4 patients, and 1 patient, respectively. There were two instances of sudden death, likely related to tumor progression. Major responses occurred in 15 of 23 patients (65%; 95% confidence interval, 43%, 85%) (1 complete response, 14 partial responses). The median survival was 8.6 months; with a median follow-up of 26 months, estimated 30-month survival was 31%. CONCLUSIONS: This regimen, although moderately toxic, has substantial activity in metastatic and regionally advanced squamous cell carcinoma of the esophagus. Further investigations should be conducted to determine the role of IFN in the treatment of esophageal carcinoma.

7/3,AB/45
DIALOG(R)File 155:MEDLINE(R)

08774068 96122910 PMID: 8535661
Phase II trial of chemotherapy, external and intraluminal radiation plus surgery for oesophageal cancer.
Beitler J J; Wadler S; Haynes H; Fell S; Rozenblit A; Wolf E; Levine B A Department of Radiation Oncology, Montefiore Medical Center, Bronx, NY, USA.
Medical oncology (Northwood, London, England) (ENGLAND) Jun 1995, 12 (2) p115-20, ISSN 1357-0560 Journal Code: 9435512
Contract/Grant No.: CA1330-23; CA; NCI
Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A pilot study was performed to assess the feasibility of combining 5-fluorouracil, recombinant alpha-2b-interferon, external radiation therapy and intraluminal high dose rate brachytherapy with surgery in patients with locally advanced esophageal carcinoma. 5-fluorouracil, 750 mg m-2, was administered via continuous 5-day infusion beginning day 1 and weekly thereafter; interferon, 10 mu subcutaneously, was administered three times per week beginning day 1 and sargramostin, 5 micrograms kg-1, was administered on days without 5-fluorouracil. External radiation began on day one using 1.5 daily fractions to 55.5 Gy. Intraluminal brachytherapy was delivered concomitantly once each week for 5 fractions of 4 Gy. None of the first eight patients went to surgery. The external radiation was changed to 1.5 Gy BID to 45 Gy followed by BID intraluminal radiation to 15 Gy. Of the last four patients, there was one case of radiation myelitis. It was found that successful surgery was not possible and excessive toxicities, including radiation myelitis, occurred with this aggressive regimen.

7/3,AB/46
DIALOG(R)File 155:MEDLINE(R)

08744467 96096774 PMID: 7493686
Effects of granulocyte-macrophage colony stimulating factor produced in Chinese hamster ovary cells (regramostim), Escherichia coli (molgramostim) and yeast (*sargramostim*) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. Hussein A M; Ross M; Vredenburgh J; Meisenberg B; Hars V; Gilbert C; Petros W P; Coniglio D; Kurtzberg J; Rubin P; et al
Duke University Bone Marrow Transplant Program, Durham, North Carolina, USA.
European journal of haematology (DENMARK) Nov 1995, 55 (5) p348-56, ISSN 0902-4441 Journal Code: 8703985
Republished from Eur J Haematol. 1995 May;54(5) 281-7; Republished from PMID 7781752
Document type: Clinical Trial; Controlled Clinical Trial; Corrected and Republished Article; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Peripheral blood progenitor cells (PBPCs) were collected without prior association with chemotherapy but after the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) produced in Chinese hamster ovary cells (CHO-GM, regramostim), Escherichia coli (E. coli-GM, molgramostim), or yeast (Yeast-GM, *sargramostim*) and used in conjunction with autologous bone marrow after high-dose chemotherapy in 69 patients with breast cancer or melanoma. The mean peripheral white blood cell (WBC) counts increased by 2.2 to 2.7-fold after regramostim, 4.5 to 7.3-fold after molgramostim and 4.3-fold after *sargramostim*. All patients underwent three leukaphereses. The mean (+/- standard error) total nucleated pheresed cells per kg x 10(8) were 4.15 +/- 0.56, 15.10 +/- 1.77 and 7.24 +/- 1.00 for patients receiving regramostim, molgramostim or *sargramostim* respectively. The mean (+/- standard error) granulocyte-macrophage colony-forming units per kg x 10(4) mobilized into the PB were 8.75 +/- 3.63, 71.03 +/- 17.85, and 65.11 +/- 18.74 for patients receiving regramostim, molgramostim, or *sargramostim* respectively. The total mean (+/- standard error) CD34+ cells per kg x 10(7) collected by three leukaphereses were 3.28 +/- 1.62, 1.34 +/- 0.51 and 2.57 +/- 1.93, for patients receiving regramostim, molgramostim or *sargramostim* respectively. The use of either molgramostim- or *sargramostim* -primed PBPCs led to complete elimination of absolute leukopenia with a WBC count under 100/mm3 in 64% and 77% of patients treated, respectively. Patients receiving molgramostim-primed PBPCs required fewer red blood cells transfusions than patients receiving regramostim-primed PBPCs (p = 0.0062). Our data indicate that PBPCs collected without prior association with chemotherapy but after either molgramostim or *sargramostim* with autologous bone marrow support and GM-CSF shorten the hematopoietic recovery after myeloablative chemotherapy in patients with breast cancer or melanoma.

7/3,AB/47
DIALOG(R)File 155:MEDLINE(R)

08689516 96057243 PMID: 7562431
Pharmacokinetics of recombinant human granulocyte-macrophage colony-stimulating factor in children after intravenous and subcutaneous administration.
Stute N; Furman W L; Schell M; Evans W E
Pharmaceutical, Department, St. Jude Children's

Research Hospital, Memphis, TN, USA.
Journal of pharmaceutical sciences (UNITED STATES) Jul 1995, 84 (7) p824-8, ISSN 0022-3549 Journal Code: 2985195R
Contract/Grant No.: CA 20180; CA; NCI; CA 21765; CA; NCI; CA 23099; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Despite its widespread use, only limited pharmacokinetic data exist for recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF), especially in children. We evaluated the pharmacokinetics of rhGM-CSF in children who had undergone intensive multiagent chemotherapy: 11 children with refractory solid tumors received 500-1500 micrograms/m2 of rhGM-CSF (*sargramostim*) as a daily 2-h intravenous (iv) infusion, and seven children received subcutaneous (sc) rhGM-CSF at 1500-2000 micrograms/m2/d in two daily injections for 2 weeks. Serum samples obtained before and after rhGM-CSF administration were analyzed for granulocyte-macrophage colony-stimulating factor (GM-CSF) by a bioassay and by ELISA. Concentrations measured by the two methods were highly correlated ($r^2 = 0.89$, $p < 0.001$). Following 2-h iv infusions, the concentration-time data were best described by a two-compartment, first-order elimination model. The median (range) for rhGM-CSF systemic clearance (CI) was 49 mL/min/m2 (range, 15-118 mL/min/m2), terminal half-life (t1/2) was 1.6 h (range, 0.9-2.5 h), and the time the GM-CSF concentration was > 1 ng/mL was 9 h (range, 6-13 h). The CI was not dose dependent or related to patient age. The absolute neutrophil count day 14 of GM-CSF was significantly related to GM-CSF dosage and platelet count on day 1. There was a weak correlation between AUC and duration of neutropenia ($p = 0.05$). The sc concentration-time data were best described by a one-compartment model with first-order absorption and elimination. Median apparent clearance was 72 mL/min/m2 (range, 27-231 mL/min/m2) and t1/2 was 2.3 h (range 0.7-3.8 h).(ABSTRACT TRUNCATED AT 250 WORDS)

7/3,AB/48
DIALOG(R)File 155:MEDLINE(R)

08626466 95384852 PMID: 7544685
Sterility of repackaged filgrastim and *sargramostim*.
Kleinberg M L
American journal of health-system pharmacy : AJHP : official journal of the American Society of Health-System Pharmacists (UNITED STATES) May 15 1995, 52 (10) p1101, ISSN 1079-2082 Journal Code: 9503023 Comment on Am J Hosp Pharm. 1994 Nov 15;51(22) 2811-2; Comment on PMID 7531941
Document type: Comment; Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/49
DIALOG(R)File 155:MEDLINE(R)

08591678 95349459 PMID: 7623728
Cyclophosphamide in combination with *sargramostim* for treatment of recurrent medulloblastoma.
Moghrabi A; Fuchs H; Brown M; Schold S C; Graham M; Kurtzberg J; Tien R; Felsberg G; Lachance D H; Colvin O M; et al
Department of Pediatrics, Hopital Sainte-Justine, Montreal, Canada. Medical and pediatric oncology (UNITED STATES) Sep 1995, 25 (3) p190-6, ISSN 0098-1532 Journal Code: 7506654
Document type: Clinical Trial; Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Thirteen patients with recurrent medulloblastoma were treated with cyclophosphamide in association with *Sargramostim*. Cyclophosphamide was given at doses ranging between 1.0-2.5 g/m2 daily for two doses. *Sargramostim* was given at a fixed dose of 250 micrograms/m2 subcutaneously twice a day beginning 24 hours after the second cyclophosphamide dose and continuing through the leukocyte nadir until the ANC was more than 1,000 cells/microliters for two consecutive days. A total of 33 courses were given with toxicity consisting of grade 4 neutropenia in all courses and grade 3-4 thrombocytopenia in 10 of 13 patients. There were no deaths related to infection or bleeding. Four patients were taken off study because of prolonged myelosuppression. Three of these patients were at the 2.5 g/m2 level, and of these three, two developed lung toxicity (grades 2 and 4, respectively). One patient developed an allergic reaction following the first injection of *Sargramostim* and was also taken off study. Of 10 evaluable patients, there were 9 PR and 1 SD. We conclude that cyclophosphamide at a dose of 2.0 g/m2/day x 2 days q 4 weeks in association with *Sargramostim* demonstrates marked activity with acceptable toxicity in patients with recurrent medulloblastoma.

7/3,AB/50
DIALOG(R)File 155:MEDLINE(R)

08541840 95300943 PMID: 7781752
Effects of granulocyte-macrophage colony stimulating factor produced in Chinese hamster ovary cells (regramostim), Escherichia coli (molgramostim) and yeast (*sargramostim*) on priming peripheral blood progenitor cells for use with autologous bone marrow after high-dose chemotherapy. Hussein A M; Ross M; Vredenburgh J;

Meisenberg B; Hars V; Gilbert C; Petros W P; Coniglio D; Kurtzberg J; Rubin P; et al

Duke University Bone Marrow Transplant Program, Durham, North Carolina, USA.

European journal of haematology (DENMARK) May 1995, 54 (5) p281-7, ISSN 0902-4441 Journal Code: 8703985

Republished in Eur J Haematol. 1995 Nov;55(5) 348-56; Republished in PMID 7493686

Document type: Clinical Trial; Controlled Clinical Trial; Journal Article Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Peripheral blood progenitor cells (PBPCs) were collected without prior association with chemotherapy but after the administration of granulocyte-macrophage colony-stimulating factor (GM-CSF) produced in Chinese hamster ovary cells (CHO-GM, regramostim), Escherichia coli (E. coli-GM, molgramostim), or yeast (Yeast-GM, *sargramostim*) and used in conjunction with autologous bone marrow after high-dose chemotherapy in 69 patients with breast cancer or melanoma. The mean peripheral white blood cell (WBC) counts increased by 2.2 to 2.7-fold after regramostim, 4.5 to 7.3-fold after molgramostim and 4.3-fold after *sargramostim*. All patients underwent three leukaphereses. The mean (+/- standard error) total nucleated pheresed cells per kg x 10(8) were 4.15 +/- 0.56, 15.10 +/- 1.77 and 7.24 +/- 1.00 for patients receiving regramostim, molgramostim or *sargramostim* respectively. The mean (+/- standard error) granulocyte-macrophage colony-forming units per kg x 10(4) mobilized into the PB were 8.75 +/- 3.63, 71.03 +/- 17.85, and 65.11 +/- 18.74 for patients receiving regramostim, molgramostim, or *sargramostim* respectively. The total mean (+/- standard error) CD34+ cells per kg x 10(7) collected by three leukaphereses were 3.28 +/- 1.62, 1.34 +/- 0.51 and 2.57 +/- 1.93, for patients receiving regramostim, molgramostim or *sargramostim* respectively. The use of either molgramostim- or *sargramostim* -primed PBPCs led to complete elimination of absolute leukopenia with a WBC count under 100/mm3 in 64% and 77% of patients treated, respectively. Patients receiving molgramostim-primed PBPCs required fewer red blood cells transfusions than patients receiving regramostim-primed PBPCs (p = 0.0062). Our data indicate that PBPCs collected without prior association with chemotherapy but after either molgramostim or *sargramostim* with autologous bone marrow support and GM-CSF shorten the hematopoietic recovery after myeloablative chemotherapy in patients with breast cancer or melanoma.

7/3,AB/51
DIALOG(R)File 155:MEDLINE(R)

08463882 95227120 PMID: 7711678

Neutropenic fever in patients after high-dose chemotherapy followed by autologous haematopoietic progenitor cell transplantation and human recombinant granulocyte-macrophage colony stimulating factor. Gluck S; Gagnon A

Northeastern Ontario Regional Cancer Centre, Sudbury, Ontario, Canada. Bone marrow transplantation (ENGLAND) Dec 1994, 14 (6) p989-90, ISSN 0268-3369 Journal Code: 8702459

Document type: Journal Article

Languages: ENGLISH

Main Citation Owner: NLM

Record type: Completed

Neutropenic fever has been one of the most difficult complications in the recovery period following high-dose chemotherapy and autologous haematopoietic progenitor cell transplantation. The differentiation between human recombinant GM-CSF (*sargramostim*)-related fever and active infection can be difficult during this observation time. In 7 of 17 patients treated for metastatic breast cancer with HDCT and PBPC within 6 consecutive months, neutropenic fever without signs of infection was observed, which may be *sargramostim* -related fever. The typical presentation must fulfil the following criteria: cyclical elevation in body temperature that happens at the predicted time after *sargramostim* administration; absence of other signs or symptoms of infections; quick resolution of the fever after onset acetaminophen administration. Having met these criteria, none of these patients has been treated with intravenous antibiotics for active infections. At the time of haematological recovery (at a median time of 13 days from PBPC reinfusion to absolute neutrophil counts of > or = 0.5/nl) the febrile episode gradually resolved. No serious complications or other side-effects were observed. No toxic deaths occurred. Only if specific symptoms or signs of infection develop, would intravenous empiric antibiotic therapy be started.

7/3,AB/52
DIALOG(R)File 155:MEDLINE(R)

08457496 95214555 PMID: 7700169

Dose escalation trial of cyclophosphamide with *Sargramostim* in the treatment of central nervous system (CNS) neoplasms.

Lachance D H; Oette D; Schold S C; Brown M; Kurtzberg J; Graham M L; Tien R; Felsberg G; Colvin O M; Moghrabi A; et al

Department of Pediatrics, Duke University Medical Center, Durham, North Carolina 27710, USA.

Medical and pediatric oncology (UNITED STATES) Apr 1995, 24 (4) p241-7, ISSN 0098-1532 Journal Code: 7506654

Document type: Clinical Trial; Journal Article

Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
We conducted a dose escalation trial of cyclophosphamide plus *Sargramostim* in the therapy of patients with newly diagnosed or recurrent central nervous system tumors. Cyclophosphamide was administered at doses ranging between 1.0 and 2.5 g/m2 daily for two doses. *Sargramostim* was administered at a fixed dose of 250 micrograms/m2 subcutaneously twice a day beginning 24 hours after the second cyclophosphamide dose and continuing through the leukocyte nadir until the absolute neutrophil count (ANC) was > 1,000 cells/microliters for two consecutive days. The MTD for patients who had not received any prior chemotherapy and who had received either no radiotherapy or radiotherapy confined to the cranium was 2.0 g/m2 daily for two doses. The MTD for patients previously treated with chemotherapy or neuraxis radiotherapy was also 2.0 g/m2 daily for two doses. Responses were seen in patients with medulloblastoma (8/9), glioblastoma multiforme (2/13), germinoma (1/1), and pineoblastoma (1/2).

7/3,AB/53
DIALOG(R)File 155:MEDLINE(R)

08443303 95215415 PMID: 7535454
Peripheral blood mononuclear mobilization with *sargramostim* (GM-CSF).
Ahmed T; Preti R A; Razis E; Farley T; Lake D E; Beer M; Cook P; Ciavarella D
New York Medical College, Valhalla.
Progress in clinical and biological research (UNITED STATES) 1994, 389 p457-62, ISSN 0361-7742 Journal Code: 7605701
Document type: Clinical Trial; Journal Article; Randomized Controlled Trial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/54
DIALOG(R)File 155:MEDLINE(R)

08402081 95159979 PMID: 7531941
Sterility of unit dose syringes of filgrastim and *sargramostim*. Singh R F; Corelli R L; Guglielmo B J
University of Iowa Hospitals and Clinics, Iowa City.
American journal of hospital pharmacy (UNITED STATES) Nov 15 1994, 51 (22) p2811-2, ISSN 0002-9289 Journal Code: 0370474
Comment in Am J Health Syst Pharm. 1995 May 15;52(10) 1101; Comment in PMID 7544685
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/55
DIALOG(R)File 155:MEDLINE(R)

08329943 95088515 PMID: 7996067
TMJ: a well-tolerated high-dose regimen for the adjuvant chemotherapy of high risk breast cancer.
Razis E D; Samonis G; Cook P; Beer M; Mittelman A; Lake D E; Feldman E J; Puccio C; Ahmed T
New York Medical College, Valhalla 10595.
Journal of medicine (UNITED STATES) 1994, 25 (3-4) p241-50, ISSN 0025-7850 Journal Code: 7505566
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Following local treatment and doxorubicin-containing standard chemotherapy, 42 patients with surgical Stage II or IIIA breast cancer containing ten or more involved axillary nodes and 13 patients with Stage IIIB disease were treated with high-dose chemotherapy (TMJ) consisting of thiotepa (750 mg/m2), mitoxantrone (40 mg/m2), and carboplatin (1000 mg/m2), with autologous bone marrow (ABM) and peripheral stem cell (PSC) transplant, followed by irradiation and/or hormone therapy. *Sargramostim* (GM-CSF) support was given to most patients. The median time to transfusion independence was two weeks. Severe non-hematologic toxicity was uncommon, with no intensive care admission or treatment-related death. At a median follow-up of 17 months, eight patients have relapsed and five have died of tumor progression. No statement can yet be made regarding adjuvant efficacy, but this high-dose regimen is very well tolerated.

7/3,AB/56
DIALOG(R)File 155:MEDLINE(R)

08100523 94230089 PMID: 10133464
Getting the most out of low-dose syringe prefilling of a high-cost biotechnology agent.
Lu A; Chan L
Hospital pharmacy (UNITED STATES) Apr 1994, 29 (4) p353, 356-7, ISSN 0018-5787 Journal Code: 0043175
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The recent increased usage of high-cost biotechnology agents has placed a tremendous impact on the hospital pharmacy budget. One approach in improving cost containment is to minimize waste during the preparation

of these agents. This is particularly practical and possible in the process of low-dose syringe repackaging of *Sargramostim* (GM-CSF) used for the treatment of neutropenia. In search of ways to reduce waste, this study looked into the dos and don'ts of repackaging this agent in syringes. Decreased waste is very significant if GM-CSF is properly reconstituted with bacteriostatic water for injection and if a syringe equipped with a permanently attached needle is used. Another 10% of the solution from each vial could be saved if the solution is withdrawn with a technique involving the vial in a right-side-up position.

7/3,AB/57
DIALOG(R)File 155:MEDLINE(R)

08099027 94218086 PMID: 8164990
Clinical implications for the administration of colony stimulating factors.
Schneider S M
Orthopaedic nursing / National Association of Orthopaedic Nurses (UNITED STATES) Jan-Feb 1994, 13 (1) p56-62, 64, ISSN 0744-6020 Journal Code: 8409486
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This article familiarizes the practitioner with the clinical nursing implications of the colony stimulating factors that have been approved for use. The process of hematopoiesis is reviewed with a focus on the mechanisms of action for *Sargramostim*, Filgrastim, and Epoetin Alfa. Each agent is discussed individually and information is presented regarding indications, pharmacologic properties, routes of administration, and potential adverse reactions. Nursing interventions for care of the patient receiving colony stimulating factors are discussed.

7/3,AB/58
DIALOG(R)File 155:MEDLINE(R)

08087550 94208756 PMID: 7512521
In vitro growth effects of colony-stimulating factors in ovarian cancer. Connor J P; Squatrito R C; Terrell K L; Antisdel B J; Buller R E Department of Obstetrics and Gynecology, University of Iowa Hospitals and Clinics, Iowa City 52242.
Gynecologic oncology (UNITED STATES) Mar 1994, 52 (3) p347-52, ISSN 0090-8258 Journal Code: 0365304
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human recombinant colony-stimulating factors may be used to treat or prevent neutropenia caused by marrow toxic chemotherapeutic agents administered to patients with cancer. Despite their common clinical use, little is known about the potential adverse effects that these cytokines may have on the growth of malignant cells. Indeed, several in vitro reports have indicated that colony-stimulating factors may act as stimulating growth factors in some human malignancies. To evaluate these effects in ovarian cancer, we investigated the possible growth effects of granulocyte colony-stimulating factor (G-CSF/Filgrastim) and granulocyte-macrophage colony-stimulating factors (GM-CSF/*Sargramostim*) on four established ovarian cancer cell lines, as well as five primary ovarian cancer cultures over a wide range of pharmacologic doses. Cell viability was measured by an ATP bioluminescence assay and expressed as a percentage of untreated control cultures. G-CSF showed no growth-stimulating effects in any of the four established cell lines tested. In the OVCAR-3 cell line, a decrease in growth (> 10%) was seen at 10, 100, and 1000 ng/ml after 5 days of continuous treatment. In the same cell line, GM-CSF caused an increase (> 10%) in growth at the same doses. However, these changes did not demonstrate statistical significance in a dose-dependent fashion. In the five primary cultures treated with G-CSF, only one demonstrated statistically significant increases in growth in a dose-dependent manner. GM-CSF treatment had no significant growth alterations in these same five primary cultures. These results would suggest that colony-stimulating factors may act as growth factors in some but not all ovarian cancer cells. Further investigations into the receptor status of ovarian cancer cells for these cytokines are underway to clarify this issue.

7/3,AB/59
DIALOG(R)File 155:MEDLINE(R)

07958642 94094263 PMID: 7505717
Drug formulary review process for *sargramostim* and filgrastim: focus on analysis of adverse drug reactions.
Kellihan M J
Division of Medical Oncology/Hematology, James Graham Brown Cancer Center, University of Louisville, Kentucky.
Clinical therapeutics (UNITED STATES) Sep-Oct 1993, 15 (5) p927-37, ISSN 0149-2918 Journal Code: 7706726
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Selection of a drug for formulary inclusion involves evaluation of safety, efficacy, and cost. The

colony-stimulating factors (CSFs) *sargramostim* and filgrastim have a broad range of potential indications and represent a costly formulary addition when acquisition price alone is considered; their comparative safety is unclear. These factors suggest that the CSFs should be closely scrutinized prior to formulary addition. In the absence of direct comparative studies, an assessment of the safety of CSFs involves evaluation of information provided in the product circular, official drug compendia, adverse biologic reports submitted to the United States Food and Drug Administration, and data from key clinical trials. Data in the product circulars report on adverse events in small numbers of patients treated for chemotherapy-induced neutropenia (filgrastim) or neutropenia subsequent to bone marrow transplantation (*sargramostim*). The official compendia and clinical trials include experience with CSFs produced in a variety of expression systems; these data are not limited to *sargramostim* and filgrastim. Importantly, there was a similar incidence of adverse events in patients who received *sargramostim* or filgrastim and in those who took placebo reported in the product circulars and the pivotal trials, suggesting that the underlying disease may have an important role in determining the side-effect profile of these agents. Adverse biologic reports represent experience with *sargramostim* and filgrastim obtained under actual clinical conditions and suggest that the same types of adverse events are seen with *sargramostim* as with filgrastim. This analysis suggests that a decision to select filgrastim over *sargramostim* for formulary inclusion based on the safety profile is not appropriate because currently available data are equivocal and that such decisions would more appropriately be based on efficacy and cost.

7/3,AB/60
DIALOG(R)File 155:MEDLINE(R)

07840099 93370417 PMID: 8362888
Strategic management of biotechnology agents.
Huber S L
Division of Pharmacy, University of Texas M.D. Anderson Cancer Center, Houston 77030.
American journal of hospital pharmacy (UNITED STATES) Jul 1993, 50 (7 Suppl 3) pS31-3, ISSN 0002-9289 Journal Code: 0370474
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The use of biologic response modifiers to demonstrate a value-driven approach to strategic management by pharmacists is described. To participate in decisions on the use of technology in their institutions, pharmacists must practice strategic management. This process includes environmental scanning, analysis of clinical and pharmacoeconomic data, and development of clinical management approaches. It is ideal for analyzing biologic response modifiers such as filgrastim and *sargramostim*. Emphasis must be placed on maximizing the fit among the products, the institution, and the health care environment. Pharmacists will find plentiful opportunities for clinical management with biotechnology agents. Practitioners who specialize in determining the total cost of care by using pharmacoeconomic methods are needed, as are practitioners trained to monitor the complicated biotechnology agents. Also, the institution needs to forecast accurately the impact of emerging biotechnology agents. If pharmacists can develop and control clinical, pharmacoeconomic, and reimbursement information databases for biotechnology agents, the pharmacy profession will be in a strong position to meet the challenges of biotechnology and realize the inherent opportunities.

7/3,AB/61
DIALOG(R)File 155:MEDLINE(R)

07840097 93370415 PMID: 7689789
Cost considerations in therapy with myeloid growth factors. Glaspy J A; Jakway J
Bowyer Oncology Center, School of Medicine, University of California, Los Angeles 90024-6956.
American journal of hospital pharmacy (UNITED STATES) Jul 1993, 50 (7 Suppl 3) pS19-26, ISSN 0002-9289 Journal Code: 0370474 Document type: Journal Article; Review; Review, Tutorial Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Costs of biologic response modifiers, specifically myeloid growth factors, are discussed relative to cost offsets they may produce in the total amount spent on health care in patients with certain disease states. Even though the biologic response modifiers granulocyte colony-stimulating factor (filgrastim) and granulocyte-macrophage colony-stimulating factor (*sargramostim* or molgramostim) are similar in name, they are chemically and biologically different. These differences result in different clinical applications. Administered after myelosuppressive antineoplastic therapy, filgrastim decreases the risk of infection. The growth factors may also be useful in patients undergoing bone marrow transplantation, in nonneutropenic patients with bacterial infections, and in patients with other disease states. Although the myeloid growth factors are somewhat expensive in terms of acquisition cost, their use is usually associated with a decrease in the risk of medical complications requiring health care expenditures, often for hospitalizations or antimicrobials. The precise cost of acquiring and administering myeloid growth factors depends on three interdependent variables: the factor used, the dosage of

the drug, and the duration of therapy. Cost offsets may be more difficult to define, but they would include direct cost offsets, such as reduced episodes of febrile neutropenia and fewer, less-intense days of hospitalization or treatment. *Sargramostim* and molgramostim have demonstrated efficacy when given after bone marrow transplantation; filgrastim has been shown to lower infection rates by at least 50% after myelosuppressive antineoplastic therapy and in patients with severe chronic neutropenia.(ABSTRACT TRUNCATED AT 250 WORDS)

7/3,AB/62
DIALOG(R)File 155:MEDLINE(R)

07840096 93370414 PMID: 7689788
Clinical effects of biologic response modifiers.
Louie S G; Jung B
Pharmacy Department, University of Southern California-Kenneth Norris Jr. Cancer Hospital, Los Angeles 90033.
American journal of hospital pharmacy (UNITED STATES) Jul 1993, 50 (7 Suppl 3) pS10-8, ISSN 0002-9289 Journal Code: 0370474
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The clinical use of the biologic response modifiers filgrastim, *sargramostim* , and regramostim is reviewed. All circulating blood cells are derived from totipotent hematopoietic stem cells. Various biologic response modifiers, including lymphokines and colony-stimulating factors, regulate and activate the lymphoid and myeloid cells of the blood. One of the more important types of blood cell for fighting infection is the neutrophil. Patients with low neutrophil concentrations are at high risk of developing neutropenic fevers and infections. The colony-stimulating factors filgrastim, *sargramostim* , and regramostim increase the production of circulating neutrophils, and this action is clinically useful in patients undergoing myelosuppressive antineoplastic therapy or bone marrow transplantation and in patients with the acquired immunodeficiency syndrome. Clinical studies of these agents in comparison with antimicrobial prophylaxis or placebo have shown a decreased rate of neutropenic-associated hospitalizations and infections. These agents are also under study for dose intensification of antineoplastics in patients with various solid tumors and for augmenting patient responses to antimicrobial therapy in situations where there is high risk of morbidity and mortality. *Sargramostim* and regramostim are both granulocyte-macrophage colony-stimulating factors that differ in their degree of glycosylation and source of production, and at high doses they can cause life-threatening adverse effects because they stimulate the production of a broad range of leukocytes. Filgrastim, which stimulates only the production of neutrophils, has been better tolerated, especially at higher doses. Biologic response modifiers hold much promise for improving therapy of certain clinical conditions by decreasing myelosuppressive complications and enhancing responses to other drugs.(ABSTRACT TRUNCATED AT 250 WORDS)

7/3,AB/63
DIALOG(R)File 155:MEDLINE(R)

07800781 93338991 PMID: 1307285
USAN Council. List No. 340. New names. *Sargramostim*. Clinical pharmacology and therapeutics (UNITED STATES) Jul 1992, 52 (1) p112, ISSN 0009-9236 Journal Code: 0372741
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/64
DIALOG(R)File 155:MEDLINE(R)

07732878 93258973 PMID: 8098278
Sargramostim for sulfasalazine-induced agranulocytosis. Rospond R M; Glowacki R C; Mailliard J A
Clinical pharmacy (UNITED STATES) Mar 1993, 12 (3) p179, ISSN 0278-2677 Journal Code: 8207437
Document type: Letter
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/65
DIALOG(R)File 155:MEDLINE(R)

07517767 93043291 PMID: 1421369
Clinical and cytogenetic responses to granulocyte-macrophage colony-stimulating factor in therapy-related myelodysplasia. Gradishar W J; Le Beau M M; O'Laughlin R; Vardiman J W; Larson R A
Department of Medicine, University of Chicago, Pritzker School of Medicine, IL.
Blood (UNITED STATES) Nov 15 1992, 80 (10) p2463-70, ISSN 0006-4971 Journal Code: 7603509
Contract/Grant No.: CA-40046; CA; NCI
Document type: Clinical Trial; Clinical Trial, Phase II; Journal Article Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We treated 10 patients with a therapy-related myelodysplastic syndrome with escalating doses of

granulocyte-macrophage colony-stimulating factor (GM-CSF; *sargramostim*) in a phase II trial and used sequential cytogenetic analyses to determine whether there was stimulation of nonclonal hematopoiesis. The GM-CSF was administered by continuous intravenous infusion over 2 hours daily for 14 days, followed by a 14-day rest period. The initial starting dose was 60 micrograms/m2/d. The GM-CSF dose was escalated within individual patients to 125 micrograms/m2, 250 micrograms/m2, and then 500 micrograms/m2/d until the peripheral blood neutrophil count at least doubled and exceeded 1,000/microL. GM-CSF treatment then continued in monthly maintenance cycles. During 57 treatment courses, the neutrophil count increased in 52 but only doubled and exceeded 1,000/microL in 21. Mild eosinophilia was stimulated in five patients, but only two had greater than 1,000 eosinophils/microL. In only three patients was any stimulation of platelet or red blood cell production observed, and thus, little change in transfusion requirements occurred. The bone marrow karyotypes from individual patients either remained completely abnormal or became increasingly abnormal over the course of treatment. We found no evidence that GM-CSF preferentially stimulated normal marrow stem cells to proliferate or had the ability to eradicate the cytogenetically abnormal clone by inducing terminal differentiation. Although the effect on granulopoiesis was transient and dependent on continued GM-CSF treatment, the increase in the neutrophil count was clinically important in some patients, allowing more effective control of ongoing infections.

7/3,AB/66
DIALOG(R)File 155:MEDLINE(R)

07352278 92293973 PMID: 1726334
Production of a monoclonal antibody (2B44) reactive on a shared epitope on dendritic reticulum cells, smooth muscle cells of vessels and Reed-Sternberg cells.
Kalidi I; Pellerain N; Masset M; Matonniere S; Valensi F; Dagay M F; Brice P; Degos L; Delsol G; Hors J
Unite INSERM U93, Hopital Saint-Louis, Paris, France.
Nouvelle revue francaise d'hematologie (GERMANY) 1991, 33 (6) p533-9 , Journal Code: 7909092
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Lymph node cells from a patient with Hodgkin's disease (HD) were cultured without Epstein-Barr virus (EBV) or *leukine* adjuvant. A cell line (719-AB) emerged from the culture after four weeks. The cell line express CD20 (79%), CD 21 (30%), CD30 (63%), CD 35 (61%) antigens and weakly CD25 (19%). using Southern Blot technique, the existence of specific EBV DNA and polyclonal immunoglobulin genes rearrangement were observed in the cell line. In order to obtain a monoclonal antibodies (MoAb), mice Balb/C were immunized with this cell line. The splenic cells suspension of immunized animals were fused with the mouse myeloma NS1. Antibody IgM kappa from secreting clones 2B44 was studied using both indirect immunofluorescence with labeled anti-mouse immunoglobulin and immunohistochemistry based on alkaline phosphatase/antiphosphatase complex (APAAP) and ModAMeX technique on a panel of normal or pathological cells. Normal peripheral lymphocytes, monocytes, polymorphonuclear cells, and erythrocytes, did not react. The MoAb 2B44 recognized the dendritic reticulum cells and the smooth muscle cells of vessels on frozen section and paraffin section from HD or reactive lymph nodes. On specially processed paraffin sections (ModAMeX) Reed-Sternberg cells (RSC) were reactive with 2B44 MoAb (in 2 cases out of 5 tested). The molecular weight of the antigen recognized by 2B44 MoAb is of 37 kd. The description of a new epitope shared by different histological components might be of interest for defining a new cluster and better understanding the nature of RSC.

7/3,AB/67
DIALOG(R)File 155:MEDLINE(R)

07277708 92206490 PMID: 1554007
Visual compatibility of *sargramostim* with selected antineoplastic agents, anti-infectives, or other drugs during simulated Y-site injection. Trissel L A; Bready B B; Kwan J W; Santiago N M
University of Texas M.D. Anderson Cancer Center, Houston. American journal of hospital pharmacy (UNITED STATES) Feb 1992, 49 (2) p402-6, ISSN 0002-9289 Journal Code: 0370474
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/68
DIALOG(R)File 155:MEDLINE(R)

07186950 92127967 PMID: 1773585
Criteria for use of *sargramostim* (granulocyte-macrophage colony-stimulating factor).
Clinical pharmacy (UNITED STATES) Dec 1991, 10 (12) p947-9, ISSN 0278-2677 Journal Code: 8207437
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

7/3,AB/69
DIALOG(R)File 155:MEDLINE(R)

07088231 92019982 PMID: 1717932
G-CSF and GM-CSF.
Scarim S K
Pediatric nursing (UNITED STATES) Sep-Oct 1991, 17 (5) p501-2, ISSN 0097-9805 Journal Code: 7505804
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Filgrastim and *sargramostim* are hematopoietic growth factors that are now produced on a large scale through recombinant DNA technology. Both agents are effective in increasing blood cell counts following chemotherapy and bone marrow transplantations. Investigational work is still being conducted to determine their potential use.
? ds

Set Items Description
S1 9321 GM()CSF
S2 13 LEUKINE
S3 71 SARGRAMOSTIM
S4 79 S2 OR S3
S5 10 S4 AND PY>2001
S6 0 S5 NOT S4
S7 69 S4 NOT S5
? s s7 and edta
69 S7
18603 EDTA
S8 0 S7 AND EDTA
? s s7 and (stabilized)
69 S7
18814 STABILIZED
S9 0 S7 AND (STABILIZED)
? s stabilized or stable
18814 STABILIZED
142632 STABLE
S10 159287 STABILIZED OR STABLE
? s edta
S11 18603 EDTA
? s s1 and s11
9321 S1
18603 S11
S12 8 S1 AND S11
? t s12/3,ab/all

12/3,AB/1
DIALOG(R)File 155:MEDLINE(R)

11190809 21240180 PMID: 11341962
Presence of a phospholipase D (PLD) distinct from PLD1 or PLD2 in human neutrophils: immunobiochemical characterization and initial purification. Horn J M; Lehman J A; Alter G; Horwitz J; Gomez-Cambronero J Department of Physiology and Biophysics, Wright State University School of Medicine, Dayton, OH 45435, USA.
Biochimica et biophysica acta (Netherlands) Jan 15 2001, 1530 (1) p97-110, ISSN 0006-3002 Journal Code: 0217513
Contract/Grant No.: HL056653; HL; NHLBI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Utilizing the transphosphatidylation reaction catalyzed by phospholipase D (PLD) in the presence of a primary alcohol and the short-chain phospholipid PC8, we have characterized the enzyme from human neutrophils. A pH optimum of 7.8-8.0 was determined. PIP(2), *EDTA*/EGTA, and ATP were found to enhance basal PLD activity in vitro. Inhibitory elements were: oleate, Triton X-100, n-octyl-beta-glucopyranoside, divalent cations, GTPgammaS and H(2)O(2). The apparent K(m) for the butanol substrate was 0.1 mM and the V(max) was 6.0 nmol mg(-1) h(-1). Immunochemical analysis by anti-pan PLD antibodies revealed a neutrophil PLD of approximately 90 kDa and other bands recognized minimally by anti-PLD1 or anti-PLD2 antibodies. The 90-kDa protein is tyrosine-phosphorylated upon cell stimulation with *GM*-*CSF* and formyl-Met-Leu-Phe. Protein partial purification using column liquid chromatography was performed after cell subfractionation. Based on the enzyme's regulatory and inhibitory factors, and its molecular weight, these data indicate an enzyme isoform that might be different from the mammalian PLD1/2 forms described earlier. The present results lay the foundation for further purification of this granulocyte PLD isoform.

12/3,AB/2
DIALOG(R)File 155:MEDLINE(R)

10433494 99420860 PMID: 10493117
Effects of *EDTA* -induced hypocalcaemia and stress on plasma TNF-alpha, IL-1-ra, G-CSF, *GM*-*CSF* and S-100 in dairy cows. Riond J L; Liesegang A; Wanner M; Kaiser C; Dobeli M; Joller-Jemelka H I Institute of Animal Nutrition, Veterinary Hospital, University of Zurich, Switzerland.
Veterinary research communications (NETHERLANDS) Aug 1999, 23 (5) p299-306, ISSN 0165-7380 Journal Code: 8100520
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The pathophysiology of postparturient paresis is still not completely understood. Knowledge recently acquired in immunology, endocrinology and cell physiology has still to be integrated in order to elucidate the aetiopathogenesis of the disease. For that purpose, the effect of the *EDTA* infusion model on the plasma concentrations of selected cytokines and growth factors, and of a calcium binding protein was examined in dairy cows. Six 6- to 11-year-old Brown Swiss cows in mid

lactation were infused with a 5% solution of Na2EDTA in one jugular vein over a period of 5 h. Blood samples were collected from the contralateral side daily two days before, and then hourly for five hours during the infusion, hourly for five hours after the end of the infusion, and once daily for 10 days thereafter. The plasma concentrations of cortisol, tumour necrosis factor-alpha, interleukin-1 receptor antagonist, granulocyte colony-stimulating factor, granulocyte and macrophage colony-stimulating factor, and the calcium binding protein S-100 were determined. Before the *EDTA* infusion, during the infusion and for two days thereafter, the mean plasma concentrations of cortisol were significantly higher than those from days 4 to 10 after the infusion. The plasma concentrations of tumour necrosis factor-alpha and interleukin-1 receptor antagonist followed a similar profile. At the end of *EDTA* infusion, low concentrations of granulocyte colony-stimulating factor were detected in one cow only. On days 3 and 4, the mean plasma concentrations of granulocyte colony-stimulating factor were significantly higher than the pre-infusion values, but this was followed by a significant decrease on post-infusion day 5. From day 4 to 7, the plasma concentrations of S-100 were significantly lower than the pre-infusion values. The importance of these findings in the pathophysiology of postparturient paresis remains to be established.

12/3,AB/3
DIALOG(R)File 155:MEDLINE(R)

09958673 98400120 PMID: 9729538
Effects of anticoagulants and temperature on expression of activation markers CD11b and HLA-DR on human leukocytes.
Shalekoff S; Page-Shipp L; Tiemessen C T
Medical Research Council AIDS Virus Research Unit, National Institute for Virology, Johannesburg, South Africa. SharonS@niv.ac.za
Clinical and diagnostic laboratory immunology (UNITED STATES) Sep 1998, 5 (5) p695-702, ISSN 1071-412X Journal Code: 9421292 Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
A whole-blood model was used to evaluate the effects of temperature and anticoagulant on the expression of activation markers HLA-DR and CD11b on peripheral leukocytes. Venous blood, anticoagulated with either *EDTA* or heparin, was obtained from six healthy blood donors and 13 hospitalized patients (8 human immunodeficiency virus type 1-seropositive individuals with concurrent pulmonary tuberculosis and 5 patients with pneumonia). A preliminary evaluation was carried out with whole blood from two of the normal donors, and cells were stained immediately for HLA-DR and CD11b markers or stained after incubation at room temperature or 37 degreesC for 18 h with or without the addition of the cytokines gamma interferon (IFN-gamma), granulocyte-macrophage colony-stimulating factor (*GM*- *CSF*), IFN-gamma plus *GM*-*CSF*, tumor necrosis factor beta, or interleukin-6. Of the cytokines tested, the combination of IFN-gamma and *GM*-*CSF* had the most pronounced modulation of marker expression on polymorphonuclear neutrophils (PMN), in particular, HLA-DR expression, which required induction for its detection. These cytokines were therefore used in further evaluations that considered the above-mentioned effects in the presence of disease. Results indicated that the expression of activation markers on PMN and lymphocytes in whole blood are influenced by the temperature of incubation and the choice of anticoagulant and the effects noted were dependent on (i) the particular cell surface marker, (ii) the cell type being studied, and (iii) the presence or absence of disease. It is therefore recommended that ex vivo whole-blood models for evaluating phenotype or immune function be carefully evaluated for the above-mentioned effects.

12/3,AB/4
DIALOG(R)File 155:MEDLINE(R)

08818160 96152533 PMID: 8573084
Granulocyte-macrophage colony-stimulating factor (*GM*-*CSF*) promotes phosphorylation and an increase in the activity of cytosolic phospholipase A2 in human neutrophils.
Nahas N; Waterman W H; Sha'afi R I
Department of Physiology, University of Connecticut Health Center, Farmington 06030-3505, USA.
Biochemical journal (ENGLAND) Jan 15 1996, 313 (Pt 2) p503-8, ISSN 0264-6021 Journal Code: 2984726R
Contract/Grant No.: AI-28810-03; AI; NIAID; HL-53786-06; HL; NHLBI Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Incubation of human neutrophils with 500 pM granulocyte-macrophage colony-stimulating factor (*GM*-*CSF*) results in a rapid and time-dependent increase in the phosphorylation of cytosolic phospholipase A2 (cPLA2), which was reflected in a slower electrophoretic mobility of the enzyme. The *GM*-*CSF* -induced phosphorylation of cPLA2 was accompanied by a parallel and time-dependent increase in the enzyme activity. Preincubation of neutrophils with the tyrosine kinase inhibitor genistein caused inhibition of the *GM*-*CSF* -stimulated phosphorylation and activity of cPLA2. Immunoprecipitation of the enzyme following incubation

of neutrophils with [32P]Pi shows that cPLA2 is phosphorylated by *GM*-*CSF* . Potato acid phosphatase caused dephosphorylation of the enzyme, indicating that cPLA2 is indeed phosphorylated by *GM*-*CSF*. The subcellular distribution of cPLA2 in *GM*-*CSF* -stimulated neutrophils revealed that the enzyme resides almost completely in the cytosolic fraction. Addition of Ca2+ to the lysis buffer before homogenization results in the translocation of the phosphorylated and the dephosphorylated forms of the enzyme to the membranes. Translocation of cPLA2 was also achieved after incubation with 0.1 microM N-formylmethionyl-leucyl-phenyl-alanine (fMLP) after *GM*- *CSF* stimulation and when neutrophils were challenged with the Ca2+ ionophore A23187. *EDTA* and EGTA were unable to solubilize the translocated enzyme from the neutrophil membranes, indicating that cPLA2 is attached to the membranes by strong bonds and not merely due to ionic forces exerted by Ca2+. The inability of *GM*-*CSF* to promote arachidonic acid mobilization is probably due to the fact that *GM*-*CSF* does not cause an increase in intracellular Ca2+, which is necessary for the translocation of the enzyme to the membranes where its substrate(s) reside.

12/3,AB/5
DIALOG(R)File 155:MEDLINE(R)

07721456 93244437 PMID: 8481520
Granulocyte-macrophage colony-stimulating factor induces sequential activation and deactivation of binding via a low-affinity IgG Fc receptor, hFc gamma RII, on human eosinophils.
Koenderman L; Hermans S W; Capel P J; van de Winkel J G
Department of Pulmonary Diseases, University Hospital Utrecht, The Netherlands.
Blood (UNITED STATES) May 1 1993, 81 (9) p2413-9, ISSN 0006-4971 Journal Code: 7603509
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Eosinophils are important in antibody-mediated immune defense against parasites based on interaction with Ig receptors (FcR). Of the three classes of IgG FcR in humans, hFc gamma RI, II, and III, solely hFc gamma RII (CD32) is expressed on freshly isolated eosinophils. Despite an expression level similar to that found on monocytes and polymorphonuclear granulocytes, binding activity of hFc gamma RII on eosinophils is constitutively low. Freshly isolated eosinophils had a negligible ability to form rosettes with IgG-sensitized erythrocytes (EA-IgG). Addition of granulocyte-macrophage colony-stimulating factor (*GM*-*CSF*) caused an approximately threefold increase in EA-IgG rosettes. This increase was maximal after 35 minutes, and declined upon further incubation at 37 degrees C. Analysis of hFc gamma RII expression levels showed no significant changes and neither was the expression of other hFc gamma R classes induced. Blocking studies with anti-Fc gamma receptor monoclonal antibody (MoAb) proved hFc gamma RII specificity of enhanced IgG complex binding. These phenomena were not restricted to *GM*-*CSF* action, because the addition of interleukin-3 or interleukin-5 similarly enhanced EA-IgG binding. The kinetics of activation of hFc gamma RII binding activity were paralleled by the binding of EA-C3bi to CR3 on eosinophils. In contrast to the stable expression of hFc gamma RII during activation with *GM*-*CSF* , CR3 expression increased slowly. Ligand binding via both types of opsonin receptors proved receptor specific. However, the kinetics of enhanced binding via hFc gamma RII and CR3 suggested the possibility of a common mechanism underlying the enhancement of ligand binding via hFc gamma RII and CR3. This hypothesis was supported by the fact that binding via hFc gamma RII proved sensitive to both high concentrations of F(ab')2 fragments of anti-CD11b MoAb MO1 and chelation of bivalent cations with *EDTA*. In conclusion, our studies indicate that cytokines can induce a transient enhancement of hFc gamma RII binding activity. Qualitative, and not quantitative, changes in this receptor appear to underly the modulation of binding activity, which may be linked to changes in CR3 activity.

12/3,AB/6
DIALOG(R)File 155:MEDLINE(R)

07391767 92324291 PMID: 1378017
GMP-140 (P-selectin/CD62) binds to chronically stimulated but not resting CD4+ T lymphocytes and regulates their production of proinflammatory cytokines.
Damle N K; Klussman K; Dietsch M T; Mohagheghpour N; Aruffo A Bristol-Myers Squibb Pharmaceutical Research Institute, Seattle, WA 98121.
European journal of immunology (GERMANY) Jul 1992, 22 (7) p1789-93, ISSN 0014-2980 Journal Code: 1273201
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
GMP-140 (P-selectin), a 140-kDa granular membrane glycoprotein localized to the alpha granules of platelets and the Weibel-Palade bodies of endothelial cells, is thought to play an important role in adhesive interactions predominantly between granulocytes, platelets and vascular endothelial cells during inflammation. Although GMP-140 binds to granulocytes, its binding to lymphocytes has not been demonstrated.

Using genetically engineered IgG C gamma 1 fusion protein of the extracellular domains of GMP-140, we demonstrate that GMP-140 binds to chronically antigen (Ag)-stimulated CD4+ T cells. Freshly isolated CD4+ T cells did not bind GMP-140, but priming and subsequent stimulation with alloantigen induced and gradually increased expression of GMP-140-reactive structures on their surface. T cells isolated from rheumatoid synovial fluids also exhibited strong binding to GMP-140. The binding of GMP-140 to primed T cells is not influenced by preactivation with phorbol 12-myristate 13-acetate, is almost completely abolished by pretreatment of T cells with neuraminidase or trypsin, and is also strongly inhibited by *EDTA*, the soluble sulfated glycans dextran sulfate, fucoidan, and heparin, but not by chondroitin sulfates. In spite of its strong binding to Ag-primed T cells, GMP-140 did not modulate the proliferative responses of these cells to various stimuli. However, GMP-140 in conjunction with anti-T cell receptor alpha beta monoclonal antibodies augmented the production of granulocyte-macrophage colony-stimulating factor *GM*-*CSF* and inhibited the production of interleukin-8 by Ag-primed T cells without influencing their tumor necrosis factor-alpha production. These results suggest that GMP-140 binds to chronically stimulated CD4+ T cells and differentially modulates their production of proinflammatory cytokines. The ability of Ag-primed T cells to bind GMP-140 may facilitate interactions with activated platelets and endothelial cells affecting the course of inflammation.

12/3,AB/7
DIALOG(R)File 155:MEDLINE(R)

07230718 92164591 PMID: 2133652
Adenosine-uridine binding factor requires metals for binding to granulocyte-macrophage colony-stimulating factor mRNA.
Malter J S; McCrory W A; Wilson M; Gillis P
Department of Pathology, Tulane University School of Medicine, New Orleans, La.
Enzyme (SWITZERLAND) 1990, 44 (1-4) p203-13, ISSN 0013-9432 Journal Code: 1262265
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Document type: Journal Article
Languages: ENGLISH
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Post-transcriptional gene regulation plays an important role in the expression of granulocyte-macrophage colony-stimulating factor (*GM*-*CSF*). Cytokine secretion by activated lymphocytes or mast cells is preceded by dramatic stabilization of the normally labile *GM*- *CSF* mRNA. The 3'-untranslated region of *GM*-*CSF* and other labile mRNAs contain the destabilizing motif adenosine-uridine-uridine-urid ine-adenosine (AUUUA). We recently identified a cytoplasmic protein denoted the adenosine-uridine binding factor (AUBF) which binds with high affinity and specificity to AUUUA elements in synthetic RNA transcripts. We now demonstrate that AUBF binds specifically to *GM*-*CSF* mRNA through the destabilizing AUUUA elements. The formation of AUBF-*GM*-*CSF* RNA complexes required calcium or magnesium which were sensitive to *EDTA* or EGTA. A variety of other divalent metals blocked magnesium-dependent AUBF activity. These observations suggest that AUBF may protect *GM*-*CSF* mRNA from rapid degradation and play a crucial role in the expression of cytokine genes.

12/3,AB/8
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06200126 89285822 PMID: 2660670
Development of a radioimmunoassay for human macrophage colony-stimulating factor (CSF-1).
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Department of Medicine, Montefiore Hospital, University of Pittsburgh, School of Medicine, Pennsylvania 15213.
Annals of the New York Academy of Sciences (UNITED STATES) 1989, 554 p156-66, ISSN 0077-8923 Journal Code: 7506858
Contract/Grant No.: R01CA15237; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Purified human urinary CSF-1 was used for production of polyclonal CSF antibodies in rabbits. The purified CSF was iodinated by a modified chloramine-T technique with retention of biologic activity. Dilutions of anti-CSF were reacted with 15,000 cpm of 125I-CSF in *EDTA*-phosphate buffer for 48 hr. Sheep antirabbit serum was added for 3 hr to precipitate the tracer-anti-CSF complex. A 1:1000 dilution of anti-CSF caused 60-90% precipitation of tracer; optimal conditions were observed with a 1:30,000 dilution. Linear displacement curves were obtained with 2-50 U of pure CSF-1. Related hormones did not cross-react in the assay; no displacement was seen with human *GM*-*CSF*, IL-1, IL-2, IL-3, EP, LH or FSH. Reactivity was also not observed with murine *GM*-*CSF* or IL-3. Ten normal human sera yielded CSF values of 91-138 U/ml in 5 assays. Urine values were 72-105 U/ml. When 32 U of pure CSF-1 was added to normal serum and urine samples, quantitative recovery was observed. Serial assays revealed a rise in serum and urinary CSF during marrow aplasia in a patient undergoing autologous BMT; CSF values returned to normal during the recovery phase. This sensitive and specific radioimmunoassay should prove useful in the further study of CSF-1 responses in vivo.

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   S14    209 PROTEIN()STABILIZATION
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Set    Items  Description
S1      9321  GM()CSF
S2        13  LEUKINE
S3        71  SARGRAMOSTIM
S4        79  S2 OR S3
S5        10  S4 AND PY>2001
S6         0  S5 NOT S4
S7        69  S4 NOT S5
S8         0  S7 AND EDTA
S9         0  S7 AND (STABILIZED)
S10   159287  STABILIZED OR STABLE
S11    18603  EDTA
S12        8  S1 AND S11
S13        0  PROTEIN()STABILIZATIO
S14      209  PROTEIN()STABILIZATION
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          209 S14
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   $24.69  Estimated total session cost   2.524 DialUnits
Logoff: level 02.05.06 D  15:00:29
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